

Novel aryne chemistry in organic synthesis

by

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For the Major Program

To my wife, Ani Qu

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LIST OF ABBREVIATIONS

Ac	acetyl
aq	aqueous
Bn	benzyl
br s	broad singlet
Bu	butyl
<i>t</i> -Bu	<i>tert</i> -butyl
BuLi	butyl lithium
°C	degree Celsius
cat.	catalytic
concd	concentrated
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
DMF	<i>N,N</i> -dimethylformamide
dt	doublet of triplets
eq	equation
equiv	equivalent
Et	ethyl
h	hour(s)
HRMS	high resolution mass spectroscopy
Hz	Hertz

IR	infrared
m	multiple
Me	methyl
mg	milligram
mL	milliliter(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
NMR	nuclear magnetic resonance
<i>o</i>	ortho
<i>p</i>	para
Ph	phenyl
q	quartet
s	singlet
satd	saturated
t	triplet
TBAC	tetra- <i>n</i> -butylammonium chloride
TBAF	tetra- <i>n</i> -butylammonium fluoride
<i>tert</i>	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

Ts

p-toluenesulfonyl

Abstract

Arynes are among the most intensively studied systems in chemistry. However, many aspects of the chemistry of these reactive intermediates are not well understood yet and their use as reagents in synthetic organic chemistry has been somewhat limited, due to the harsh conditions needed to generate arynes and the often uncontrolled reactivity exhibited by these species. Recently, *o*-silylaryl triflates, which can generate the corresponding arynes under very mild reaction conditions, have been found very useful in organic synthesis. This thesis describes several novel and useful methodologies by employing arynes, which generate from *o*-silylaryl triflates, in organic synthesis.

An efficient, reliable method for the *N*-arylation of amines, sulfonamides and carbamates, and the *O*-arylation of phenols and carboxylic acids is described in Chapter 1. Amines, sulfonamides, phenols, and carboxylic acids are good nucleophiles, which can react with arynes generated from *o*-silylaryl triflates to afford the corresponding *N*- and *O*-arylated products in very high yields. The regioselectivity of unsymmetrical arynes has also been studied. A lot of useful, functional groups can tolerate our reaction conditions.

Carbazoles and dibenzofurans are important heteroaromatic compounds, which have a variety of biological activities. A variety of substituted carbazoles and dibenzofurans are readily prepared in good to excellent yields starting with the corresponding *o*-iodoanilines or *o*-iodophenols and *o*-silylaryl triflates by a treatment with CsF, followed by a Pd-catalyzed cyclization, which overall provides a one-pot, two-step process. By using this methodology, the carbazole alkaloid mukonine has been concisely synthesized in a very good yield.

Insertion of an aryne into a σ -bond between a nucleophile and an electrophile (Nu-E) should potentially be a very beneficial process from the standpoint of organic synthesis. A

variety of substituted ketones and sulfoxides have been synthesized in good yields via the intermolecular C-N σ -bond addition of amides and S-N σ -bond addition of sulfinamides to arynes under mild reaction conditions.

The indazole moiety is a frequently found subunit in drug substances with important biological activities. Indazole analogues have been readily synthesized under mild reaction conditions by the [3+2] cycloaddition of a variety of diazo compounds with *o*-silylaryl triflates in the presence of CsF or TBAF.

Polycyclic aromatic and heteroaromatic hydrocarbons have been synthesized in high yields by two different processes involving the Pd-catalyzed annulation of arynes. Both processes appear to involve the catalytic, stepwise coupling of two very reactive substrates, an aryne and an organopalladium species, to generate excellent yields of cross-coupled products.

GENERAL INTRODUCTION

Although arynes have historically received much attention from physical organic chemists, their use as reagents in synthetic organic chemistry has been somewhat limited, due to the harsh conditions needed to generate arynes and the often uncontrolled reactivity exhibited by these species. Recently, *o*-silylaryl triflates, which can generate the corresponding arynes under very mild reaction conditions, have been found very useful in organic synthesis.

Establishing an efficient, reliable method for the *N*-arylation of amines, sulfonamides and carbamates, and the *O*-arylation of phenols and carboxylic acids is currently a very active area of research in organic synthesis. Amines, sulfonamides, phenols, and carboxylic acids are good nucleophiles, which can directly react with arynes to generate the corresponding *N*- and *O*-arylated products. An efficient, transition-metal free procedure for the *N*-arylation of amines, sulfonamides and carbamates and the *O*-arylation of phenols and carboxylic acids has been achieved by allowing these substrates to react with a variety of *o*-silylaryl triflates in the presence of CsF as described in Chapter 1.

An efficient route to a variety of carbazoles and dibenzofurans has been described in Chapter 2. It involves the reaction of *o*-iodoanilines or *o*-iodophenols with *o*-silylaryl triflates in the presence of CsF to afford the *N*- or *O*-arylated products, which are subsequently cyclized using a Pd catalyst to carbazoles and dibenzofurans in good to excellent yields. By using this methodology, the carbazole alkaloid mukonine has been synthesized in a very good yield.

The direct addition of a C-N σ -bond of amides and the S-N σ -bond of sulfinamides to triple bonds is not easy. An efficient, mild, transition metal-free method has been developed

for the intermolecular C-N σ -bond addition of amides and S-N σ -bond addition of sulfinamides to arynes to form one new C-C bond and one new heteroatom-carbon bond in one step at room temperature as described in Chapter 3. Evidence for a stepwise mechanism is provided. This chemistry tolerates a variety of functional groups.

The indazole moiety is a frequently found subunit in drug substances with important biological activities. The [3+2] cycloaddition of a variety of diazo compounds with *o*-silylaryl triflates in the presence of CsF or TBAF affords a wide variety of indazoles in good to excellent yields as described in Chapter 4.

Transition metal-catalyzed annulation processes have proven very useful in organic synthesis. Such annulation processes have not previously been extended to arynes, because arynes are very reactive substrates compared to ordinary alkynes and they readily undergo cyclotrimerization under transition metal catalysis to form polycyclic aromatic hydrocarbons. Polycyclic aromatic and heteroaromatic hydrocarbons have been synthesized in high yields by two different processes involving the Pd-catalyzed annulation of arynes as described in Chapter 5. Both processes appear to involve the catalytic, stepwise coupling of two very reactive substrates, an aryne and an organopalladium species, to generate excellent yields of cross-coupled products.

Dissertation Organization

This dissertation is divided into five chapters. Each of the chapters presented herein is written by following the guidelines for a full paper in the *Journal of Organic Chemistry* and is composed of the abstract, introduction, results and discussion, conclusion, experimental section, and references.

Chapter 1 discusses an efficient, transition-metal free procedure for the *N*-arylation of amines, sulfonamides and carbamates and *O*-arylation of phenols and carboxylic acids by allowing these substrates to react with a variety of *o*-silylaryl triflates in the presence of CsF.

Chapter 2 reports the Pd-catalyzed, one-pot, two-step synthesis of a variety of carbazoles and dibenzofurans starting with the corresponding *o*-iodoanilines or *o*-iodophenols and *o*-silylaryl triflates.

Chapter 3 presents an efficient, mild, transition metal-free method for the intermolecular C-N σ -bond addition of amides and S-N σ -bond addition of sulfinamides to arynes to form one C-C bond and one heteroatom-carbon bond in one step at room temperature. Evidence for a stepwise mechanism is provided.

Chapter 4 reports the [3+2] cycloaddition of a variety of diazo compounds with arynes generated from *o*-silylaryl triflates in the presence of CsF or TBAF. This process affords a wide variety of indazoles in good to excellent yields.

Chapter 5 describes a novel palladium-catalyzed annulation of arynes by aryl halides, which provides a novel way to synthesize a variety of polycyclic aromatic and heteroaromatic hydrocarbons in good yields. Evidence for a stepwise mechanism is provided.

Finally, all of the ^1H and ^{13}C NMR spectra for the new starting materials and reaction products have been compiled in appendices A-E following the general conclusions for this dissertation.

CHAPTER 1. Facile *N*-Arylation of Amines and Sulfonamides and *O*-Arylation of Phenols and Arenecarboxylic Acids

Based on a paper published in the *Journal of Organic Chemistry*⁷⁷

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Abstract

An efficient, transition-metal free procedure for the *N*-arylation of amines, sulfonamides and carbamates and *O*-arylation of phenols and carboxylic acids has been achieved by allowing these substrates to react with a variety of *o*-silylaryl triflates in the presence of CsF. An aryne intermediate is involved in this chemistry. Good to excellent yields of arylated products are obtained under very mild reaction conditions. This chemistry readily tolerates a variety of functional groups.

Introduction

Establishing an efficient, reliable method for the *N*-arylation of amines, sulfonamides and carbamates, and the *O*-arylation of phenols and carboxylic acids is currently a very active area of research in organic synthesis. Such aryl subunits are commonly found in a variety of biologically active and natural compounds,¹ agrochemicals,² HIV-1 protease inhibitors,³ and compounds of interest in material science.⁴ Traditionally, the *N*-arylation of amines and *O*-arylation of phenols have been carried out under copper-mediated Ullmann-type conditions involving the coupling of amines and phenols with aryl halides.⁵ Although these copper-promoted reactions are useful, they usually require harsh reaction conditions and

stoichiometric amounts of copper, and the yields are not very reproducible.⁶ Recently, a number of valuable new methods have been developed for the *N*-arylation of amines and sulfonamides, and the *O*-arylation of phenols and carboxylic acids.⁷ Buchwald⁸ and Hartwig⁹ have demonstrated that the Cu- or Pd-catalyzed *N*-arylation of a variety of amines and *O*-arylation of phenols by aryl halides is a powerful method for the synthesis of arylamines and diaryl ethers. Evans¹⁰ and Chan¹¹ have independently reported the synthesis of diaryl ethers by the copper(II)-promoted cross-coupling of phenols and aryl halides.

Despite these significant recent improvements, there still are limitations in present *N*- and *O*-arylation methods. For example, (1) it is still difficult to prepare *N*-arylated sulfonamides¹² and present *N*-arylation methodology may not accommodate certain organic functionality. Of the functional groups that are incompatible with the Cu- or Pd-catalyzed *N*-arylation methodology, the most important are probably halides, sulfonates,¹³ hydroxyl groups¹⁴ and probably carbon-carbon triple bonds. (2) Phenols can smoothly be converted to diaryl ethers only if no strong electron-withdrawing group is present.^{7a,b} (3) Most reaction conditions are fairly harsh, usually requiring high temperatures (>110 °C), and strong polar and often toxic solvents.

The direct coupling of aromatic carboxylic acids and aryl halides or the carbonylation of aryl halides using a palladium catalyst to generate the corresponding aryl esters is difficult.¹⁵ The direct esterification of phenols by aliphatic or aromatic carboxylic acids is virtually impossible due to the poor nucleophilicity of phenols.¹⁶ In the classical methods for esterification, a strong acid, such as sulfuric acid, is needed, which is not suitable for acid sensitive compounds, can be corrosive, and often produces side reactions, such as carbonization, oxidation, etc.¹⁷ Recently, we have reported an efficient and reliable

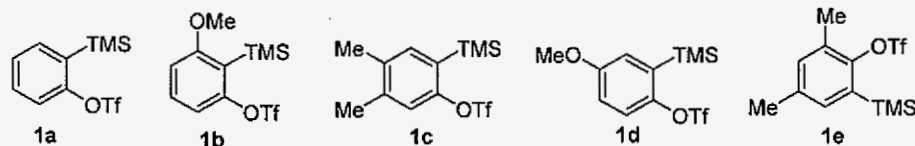
procedure to *N*-arylate amines and sulfonamides and *O*-arylate phenols and carboxylic acids under mild reaction conditions, which can tolerate a wide variety of functional groups, including halide, ester, amide, hydroxyl, nitro, aldehyde, and ketone groups.

Recently, silylaryl triflate **1a**¹⁸ has been employed to generate benzyne under very mild reaction conditions, which can easily undergo a variety of synthetically useful nucleophilic¹⁹ and cycloaddition reactions.²⁰ However, the arylation of amines,²¹ sulfonamides, phenols and carboxylic acids by arynes has not been widely studied due to the difficulty in generating arynes under convenient reaction conditions. Very recently, we reported that the reaction of a variety of amines, sulfonamides, carbamates, phenols and carboxylic acids with arynes generated from a variety of silylaryl triflates under very mild reaction conditions provides excellent yields of arylated products, while tolerating many functional groups.²² Herein, we wish to report the full details of this very efficient arylation procedure and our studies on the regioselectivity of addition to a number of unsymmetrical substituted silylaryl triflates.

Results and Discussion

Preparation of the Aryne Precursors.

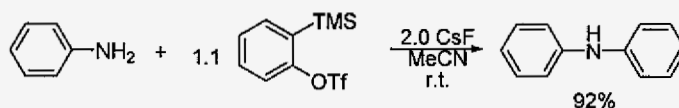
The arynes **1a-1e** were selected as substrates for our experiments. Aryne precursor **1a** was selected as the simplest and most readily available aryne to study the scope of this chemistry. Aryne precursors **1b**, **1d** and **1e** were selected to study the regioselectivity of the arylation procedure. The synthesis of silylaryl triflates **1a**,¹⁸ **1b**,²³ **1c**,^{19c} and **1d**²⁴ has already been reported, and the precursor **1e**²⁵ can easily be prepared by a similar three-step procedure from the corresponding 2-bromo-4,6-dimethylphenol.



N-Arylation of Aromatic Amines.

Our initial studies focused on achieving optimal reaction conditions for the *N*-arylated product using aniline and silylaryl triflate **1a** as the model system. We first allowed 2-(trimethylsilyl)phenyl triflate (**1a**) to react with 2.0 equiv of CsF and 1.2 equiv of aniline in MeCN at room temperature for 20 h. Diphenylamine was obtained in an 81% yield and only a trace of triphenylamine was isolated. After trying several reactions, we found that THF was also a good solvent for the *N*-arylation of aniline and CsF can be replaced by *n*-Bu₄NF (TBAF). Although the reaction time can be dramatically decreased to 30 mins when TBAF is allowed to react with the silylaryl triflate **1a** to generate benzyne, the yield is a little lower. The optimal reaction conditions thus far developed employ 0.25 mmol of aniline, 1.1 equiv of silylaryl triflate **1a** and 2.0 equiv of CsF in MeCN at room temperature for 10 h. Diphenylamine was obtained in a 92% yield (Scheme 1) (Table 1, entry 1).

Scheme 1



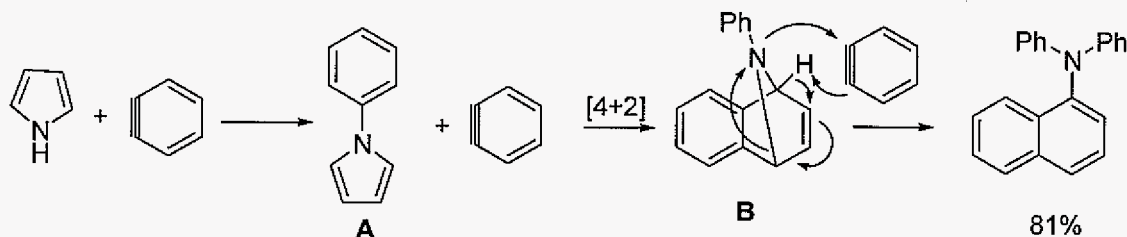
We next studied the scope of this methodology by allowing a wide variety of aromatic amines to react with the silylaryl triflates **1a**, **1b**, and **1c**.²⁶ The results are summarized in Table 1. Aniline itself and aniline with electron-donating and -withdrawing groups (Table 1, entries 1 and 3-8), such as nitro, cyano, ester, ketone, amide and methoxy groups, all react well with silylaryl triflate **1a** and CsF to afford excellent yields of the desired phenyl-substituted products. It is noteworthy that haloanilines also react with silylaryl triflate **1a** to

generate the desired halo-substituted products in excellent yields (Table 1, entries 9-11). Halides, which are unlikely to survive under the Pd-mediated amination reaction conditions,^{8,9} are readily accommodated by our reaction conditions. When sterically-hindered amines are used as the starting materials (Table 1, entries 12 and 13), good yields of the *N*-arylated products are still obtained.

Secondary amines usually react faster than primary amines with the silylaryl triflates plus CsF (Table 1, entries 14 and 16-19), except when silylaryl triflate **1c** is employed (Table 1, entry 15), and excellent yields are generally obtained. It appears that generation of the aryl anion is significantly slower using the silylaryl triflate **1c**.²⁷

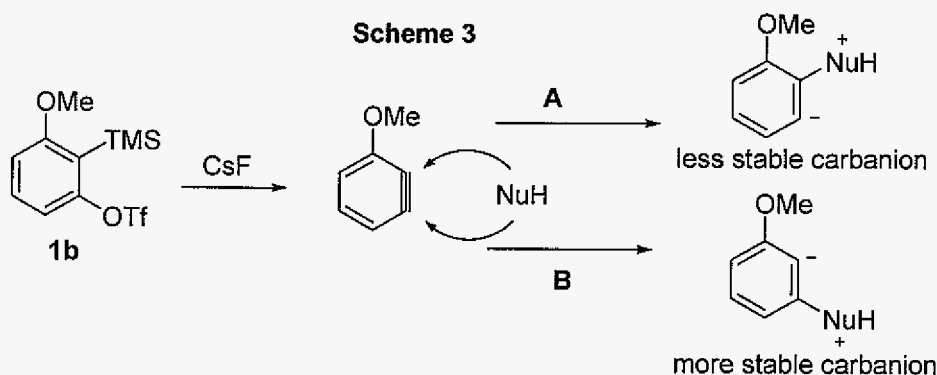
Diarylation products are also readily obtained in excellent yields when an excess of the silylaryl triflate is employed with primary aromatic amines (Table 1, entries 20-23 and 25). However, the sterically-hindered aniline *o*-*t*-butylaniline afforded only the monoarylated product, even when an excess of the silylaryl triflate **1a** was employed (Table 1, entry 24). While imidazole affords a high yield of the *N*-arylated product (entry 26), 1-(diphenylamino)naphthalene is obtained in an 81% yield, when pyrrole is allowed to react with 3.3 equiv of silylaryl triflate **1a** (Table 1, entry 27).²⁸ This unexpected product can be explained by the mechanism shown in Scheme 2. First pyrrole reacts with benzyne to generate the *N*-arylated compound **A**, which then undergoes [4+2] cycloaddition to afford compound **B**, which can apparently react further with one more equivalent of benzyne to afford the 1-(diphenylamino)naphthalene in an 81% yield. The *N*-arylation of benzotriazole proceeded in high yield, but afforded a 1:3.5 mixture of N-2 and N-1 arylation products respectively. This result is similar to results obtained using the Pd-catalyzed amination chemistry (Table 1, entry 28).²⁹

Scheme 2



The regiochemistry of the substitution reaction using unsymmetrical arynes has proven quite interesting. The methoxy-substituted silylaryl triflate **1b** reacts cleanly with aniline to generate a single regioisomer of either the monoarylation or diarylation products in good yields (Table 1, entries 2 and 21). When methoxy-substituted silylaryl triflate **1d** is employed with *N*-methylaniline, two isomers were obtained in almost equal amounts (Table 1, entry 16). The very different regioselectivity observed using these two arynes can be readily explained by steric and electronic effects. The use of silylaryl triflate **1b** favors nucleophilic attack at the position meta to the methoxy group of the aryne (Scheme 3, path B).³⁰ When using silylaryl triflate **1d**, the steric and electronic effects are very similar in the meta and para positions to the methoxy group of the aryne.

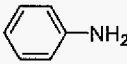
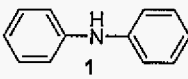
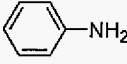
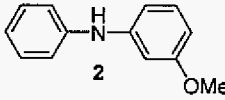
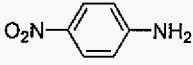
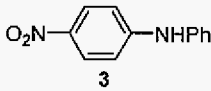
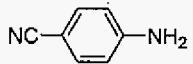
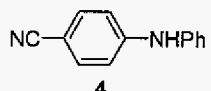
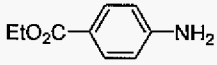
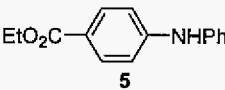
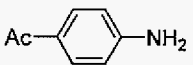
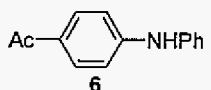
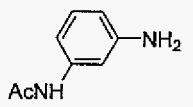
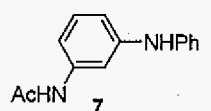

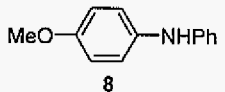
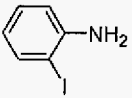
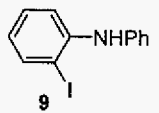
Scheme 3

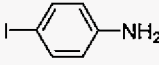
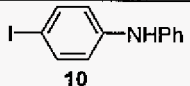
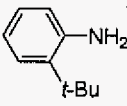
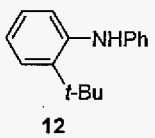
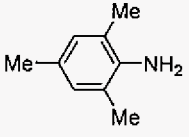
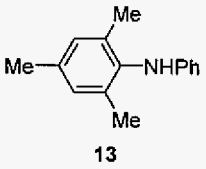
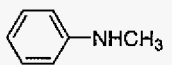
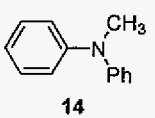
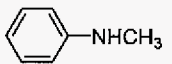
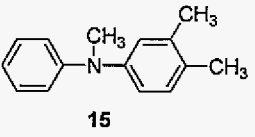
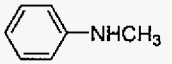
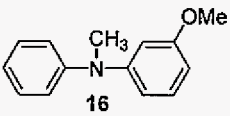
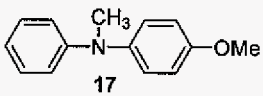
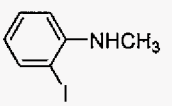
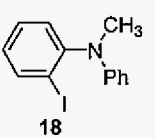
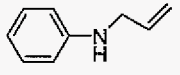
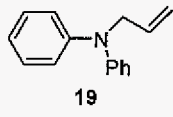
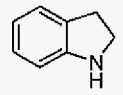
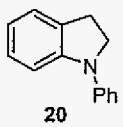


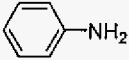
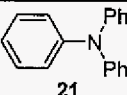
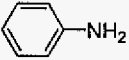
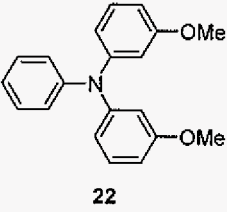
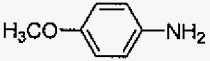
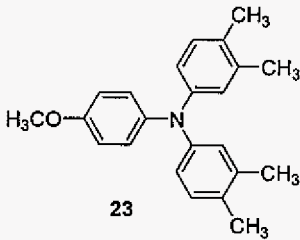
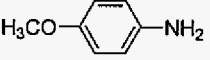
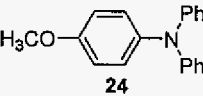
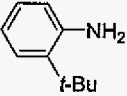
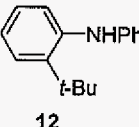

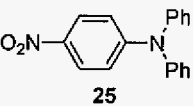

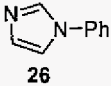

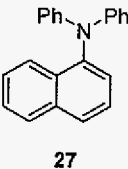
In summary, from Table 1, one can see that almost all aromatic amines react well with silylaryl triflates and CsF under very mild reaction conditions to afford good to excellent yields of the desired products. Furthermore, one can selectively prepare secondary or tertiary

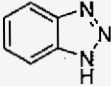
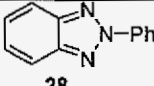
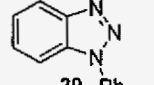
arylamines by simply changing the ratio of the reactants (compare entries 1 and 21, and 8 and 23).

Table 1. Facile *N*-Arylation of Aromatic Amines^a

entry	amine	silylaryl triflate (equiv)	CsF (equiv)	time (h)	product	% isolated yield
1		1a (1.1)	2.0	10		92
2		1b (1.1)	2.0	10		94
3		1a (1.1)	2.0	10		85
4		1a (1.1)	2.0	10		90
5		1a (1.1)	2.0	10		94
6		1a (1.1)	2.0	10		94
7		1a (1.1)	2.0	10		95
8		1a (1.1)	2.0	10		89 ^b
9		1a (1.1)	2.0	10		91

10		1a (1.1)	2.0	10		92
12		1a (1.1)	2.0	10		77
13		1a (1.1)	2.0	10		90
14		1a (1.1)	2.0	5		96
15		1c (1.1)	2.0	10		97
16		1d (1.1)	2.0	5		94 (1:1)
						
17		1a (1.1)	2.0	5		97
18		1a (1.1)	2.0	5		97
19		1a (1.1)	2.0	5		97

20		1a (2.4)	4.0	72		98
21		1b (2.4)	4.0	72		94
22		1c (2.4)	4.0	72		93
23		1a (2.4)	4.0	72		100
24		1a (2.4)	4.0	72		81 ^c
25		1a (2.4)	4.0	72		55 ^d
26		1a (1.2)	2.0	24		76
27		1a (3.6)	6.0	72		81

28		1a (1.2)	2.0	24	 	92 (1 : 3.5)
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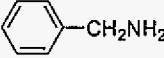
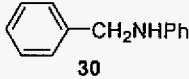
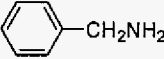
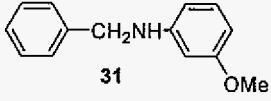
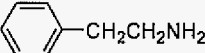
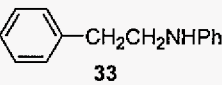
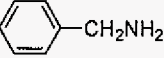
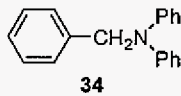
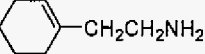
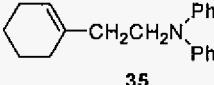
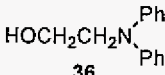
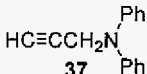
^a All reactions were run under the following reaction conditions, unless otherwise specified: 0.25 mmol of amine and the indicated amount of silylaryl triflate and CsF were stirred in 4 mL of MeCN at room temperature. ^b A 4% yield of the diarylated product was obtained. ^c Only monoarylated product was obtained. ^d A 40% yield of monoarylated product was obtained.

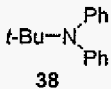

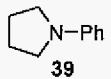

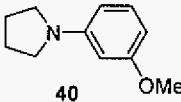

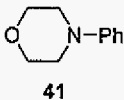
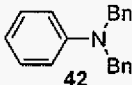
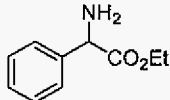
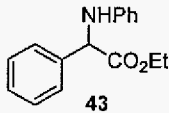
***N*-Arylation of Alkyl Amines.**

Alkylamines also react well with the silylaryl triflates and CsF to afford mono or diarylated alkylamines in good to excellent yields under very mild reaction conditions. The results are summarized in Table 2. The mono *N*-arylation of primary alkylamines is accomplished in fairly good yield when allowing an excess of the primary alkylamine to react with the silylaryl triflate and CsF, although about 10% of the diarylated product is also usually obtained (Table 2, entries 1-4). When an excess of the silylaryl triflate and CsF is employed with primary amines or secondary amines, tertiary amines can be obtained in excellent yields (Table 2, entries 5-13). Even sterically hindered *t*-BuNH₂ affords an excellent yield of the diarylated product. The silylaryl triflate **1a** can also selectively react with an amino group in the presence of an alcohol group to afford the corresponding *N*-arylation product in an 83% yield, although 8% of the *O*-arylation product *N*-(2-phenoxyethyl)-*N*-phenylaniline was isolated as a side product (entry 7). An amino ester has also proven to be a good substrate for *N*-arylation (Table 2, entry 14). Alcohols, and carbon-carbon double and triple bonds are readily accommodated by this process. It should be

pointed out that a variety of other functional groups, including halide and ester groups, should be readily tolerated under our reaction conditions.

Table 2. Facile *N*-Arylation of Alkylamines^a

entry	amine	silylaryl triflate (equiv)	CsF (equiv)	time (h)	product	% isolated yield
1		1a (0.9)	2.0	5	 30	70 ^b
2		1b (0.9)	2.0	5	 31	71 ^b
3	HC≡CCH ₂ NH ₂	1a (0.9)	2.0	5	HC≡CCH ₂ NHPh 32	62 ^c
4		1a (0.9)	2.0	5	 33	66 ^b
5		1a (2.4)	4.0	72	 34	97
6		1a (2.4)	4.0	72	 35	99
7	HOCH ₂ CH ₂ NH ₂	1a (2.4)	4.0	72	 36	83 ^d
8	HC≡CCH ₂ NH ₂	1a (2.4)	4.0	72	 37	78

9	$t\text{-Bu-NH}_2$	1a (2.4)	4.0	72		96
10		1a (1.2)	2.0	5		95
11		1b (1.2)	2.0	5		97
12		1a (1.2)	2.0	5		81
13	$(\text{Bn})_2\text{NH}$	1a (1.2)	2.0	5		99
14		1a (1.2)	2.0	5		65

^a All reactions were run under the following reaction conditions, unless otherwise specified: 0.25 mmol of the amine and the indicated amount of silylaryl triflate and CsF were stirred in 4 mL of MeCN at room temperature.

^b Approximately a 10% yield of the diarylated product was obtained. ^c A 12% yield of the diarylated product was obtained. ^d An 8% yield of *N*-(2-phenoxyethyl)-*N*-phenylaniline was also obtained.

N-Arylation of Sulfonamides and Carbamates.

While some effort has been devoted recently to the *N*-arylation of sulfonamides,³¹ the scope of this chemistry with respect to either the sulfonamide or the aryl halide is still very limited. As shown in Table 3, entries 1-13, alkane- and arenesulfonamides both efficiently undergo *N*-arylation under our reaction conditions. Using primary sulfonamides and an excess of silylaryl triflate, one obtains the corresponding diarylation product in high yield in

a fairly short reaction time compared with the times required for the *N*-arylation of amines. Again, a variety of functional groups, including iodine, chloride, and ester groups, are tolerated under our reaction conditions. Both electron-donating and electron-withdrawing groups on the arene moiety of the arenesulfonamide give excellent yields (Table 3, entries 4-8). Interestingly, *p*-aminobenzenesulfonamide reacts with 3.3 equiv of silylaryl triflate **1a** to afford a product with a monoarylated amine and the diarylated sulfonamide (Table 3, entry 9). It is important to point out that we cannot obtain monoarylation products of primary sulfonamides under our reaction conditions, even when one uses an excess of the sulfonamide. One can also start with secondary sulfonamides and produce the corresponding *N*-arylated tertiary sulfonamides in excellent yields (Table 3, entries 10-13). The methoxy-substituted silylaryl triflate **1b** also reacts cleanly with *N*-methyl-*p*-toluenesulfonamide to afford a high yield and excellent regioselectivity (Table 3, entry 11).³⁰ Only the product of substitution meta to the methoxy substituent is observed. Saccharin also reacts well with silylaryl triflate **1a** to afford the *N*-arylated product in a 72% yield (Table 3, entry 14).

We have also investigated the use of carboxamides to generate *N*-arylamides from the silylaryl triflate **1a** and CsF at room temperature. Unfortunately, only a trace of the corresponding *N*-arylamide could be obtained from benzamide (Table 3, entry 15). Simple amides are apparently neither acidic enough to form the corresponding anion or nucleophilic enough to directly attack the aryne. However, one can obtain a 60% yield of *N*-arylation product from phthalimide (Table 3, entry 16). However, *N*-arylcarbamates react well with the silylaryl triflate **1a**, affording the *N*-arylation products in excellent yields in 5 h (Table 3, entries 17 and 18). Note that once again iodine and chloride groups are readily accommodated by this process.

Table 3. Facile *N*-Arylation of Sulfonamides and Carbamates^a

entry	sulfonamides	silylaryl triflate (equiv)	CsF (equiv)	time (h)	product	% isolated yield
1		1a (2.4)	4.0	24		80
2		1a (2.4)	4.0	24		78
3		1a (2.4)	4.0	24		99
4		1a (2.4)	4.0	24		100
5		1b (2.4)	4.0	24		92
6		1a (2.4)	4.0	24		99
7		1a (2.4)	4.0	24		100

10		1a (1.2)	2.0	24		87
11		1b (1.2)	2.0	12		91
12		1a (1.2)	2.0	12		94
13		1a (1.2)	2.0	12		98
14		1a (1.2)	2.0	12		72
15		1a (1.2)	2.0	24		0
16		1a (1.2)	2.0	12		60
17		1a (1.2)	2.0	5		96
18		1a (1.2)	2.0	5		93

^a All reactions were run under the following reaction conditions, unless otherwise specified: 0.25 mmol of the sulfonamide or amide and the indicated amount of silylaryl triflate and CsF were stirred in 3 mL of MeCN at room temperature.

***O*-Arylation of Phenols.**

After our success with the *N*-arylation of amines, sulfonamides and carbamates under very mild reaction conditions, it was natural for us to investigate the *O*-arylation of phenols and carboxylic acids using silylaryl triflates and CsF. We first examined the reaction of phenol with 1.2 equiv of 2-(trimethylsilyl)phenyl triflate (**1a**) and 2 equiv of CsF in MeCN at room temperature, our standard reaction conditions for the *N*-arylation of amines and sulfonamides. We obtained only a 66% yield of the desired diphenyl ether in 20 h. After optimizing this reaction system using phenol and 1.5 equiv of silylaryl triflate **1a** plus 3.0 equiv of CsF in MeCN for 1 d at room temperature, we were able to obtain diphenyl ether in a 92% isolated yield (Table 4, entry 1).

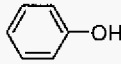
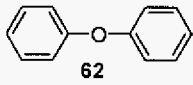
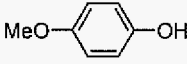
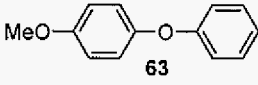
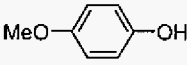
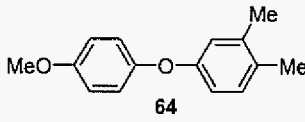
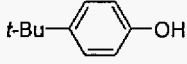
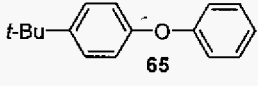
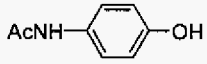
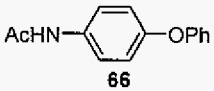
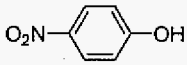
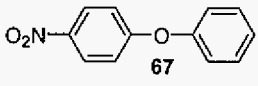
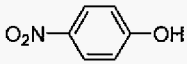
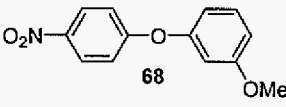
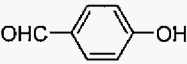
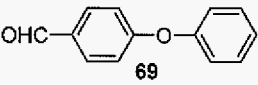
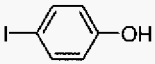
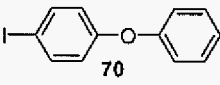
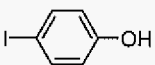
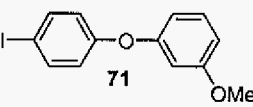
Using these optimal reaction conditions, this method has been applied to the *O*-arylation of a wide variety of phenols. The results are summarized in Table 4. Phenol itself and a phenol with an electron-donating methoxy group react well with silylaryl triflate **1a** to give the corresponding diaryl ethers in high yields (Table 4, entries 1 and 2). If 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1c**) is allowed to react with *p*-methoxyphenol, we can obtain the corresponding diaryl ether in a 93% yield (Table 4, entry 3). *p*-*tert*-Butylphenol also works well, affording the corresponding *O*-arylated product in an 85% yield (Table 4, entry 4). One still can obtain a 91% yield of the *O*-arylated product from phenol bearing an acetamide group (Table 4, entry 5). This result is consistent with our

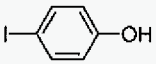
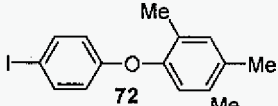
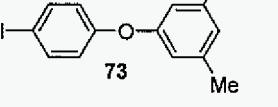
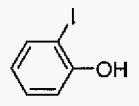
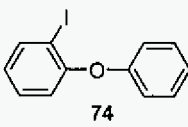
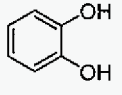
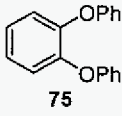
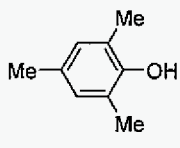
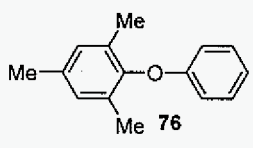
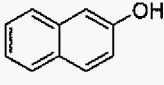
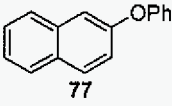
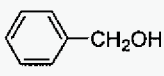
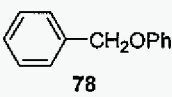
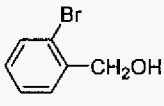
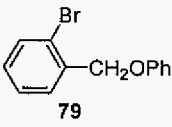
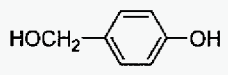
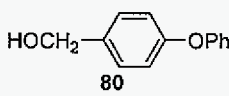
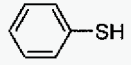
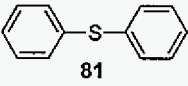
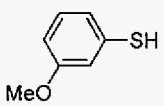
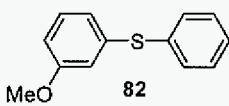
earlier observation that simple amides do not readily undergo *N*-arylation. Phenols bearing an electron-withdrawing substituent generally behave poorly or are completely inert towards diaryl ether formation when using aryl halides and a Pd catalyst to effect *O*-arylation.^{8e,f} However, under our reaction conditions, phenols with an electron-withdrawing group, such as a nitro or aldehyde group, work quite well to generate the corresponding diaryl ethers in high yields (Table 4, entries 6-8). When *ortho*- or *para*-substituted iodophenol were employed, one can still obtain the corresponding *O*-arylated phenols in over 90% yields (Table 4, entries 9-12). The analogous reaction with silylaryl triflate **1c** affords two isomers, compounds **72** and **73**, in a 1:1.5 ratio (Table 4, entry 11). This is easily explained by steric effects. Clearly, nucleophiles prefer reacting at the position *meta* to the methyl group, rather than *ortho* to the methyl group.¹⁹ Interestingly, if we use 1,2-benzenediol, we obtain a 72% yield of the double *O*-arylation product (Table 4, entry 13). The sterically hindered phenol 2,4,6-trimethylphenol also reacts smoothly with silylaryl triflate **1a** to afford a 68% yield of the desired product. With β -naphthol, one can obtain the *O*-arylated product in an 84% yield (Table 4, entry 15).

In general, alcohols do not react with these arynes to give good yields of aryl ethers. For example, benzyl alcohol afforded only a 25% yield of the corresponding aryl ether, even when a stronger base, such as DBU, was added (Table 4, entry 16). *o*-Bromobenzyl alcohol gave a slightly better yield of 36% (Table 4, entry 17). Consistent with these results, 4-hydroxybenzyl alcohol reacts with silylaryl triflate **1a** to afford 4-phenoxybenzyl alcohol in a 75% yield (Table 4, entry 18). Arene thiols also react well with silylaryl triflate **1a** to afford the *S*-arylated product in a fairly good yield (Table 4, entries 19 and 20). This chemistry provides a very convenient method to prepare a wide variety of diaryl ethers and sulfides that

tolerates a number of functional groups and produces very high yields under very mild reaction conditions.

Table 4. Facile *O*-Arylation of Phenols^a

entry	phenol	silylaryl triflate (equiv)	CsF (equiv)	time (h)	product	% isolated yield
1		1a (1.5)	3.0	24	 62	92
2		1a (1.5)	3.0	24	 63	98
3		1a (1.5)	3.0	24	 64	93
4		1a (1.5)	3.0	24	 65	85
5		1a (1.5)	3.0	24	 66	91
6		1a (1.5)	3.0	24	 67	96
7		1a (1.5)	3.0	24	 68	96
8		1a (1.5)	3.0	24	 69	91
9		1a (1.5)	3.0	24	 70	94
10		1a (1.5)	3.0	24	 71	95

11		1e (1.5)	3.0	24	 72	92 (1 : 1.5)
					 73	
12		1a (1.5)	3.0	24	 74	90
13		1a (3.0)	6.0	60	 75	72
14		1a (1.5)	3.0	24	 76	68
15		1a (1.5)	3.0	24	 77	84
16		1a (1.5)	3.0	24	 78	25 ^b
17		1a (1.5)	3.0	24	 79	36
18		1a (1.5)	3.0	24	 80	75
19		1a (1.5)	3.0	24	 81	70
20		1a (1.5)	3.0	24	 82	66

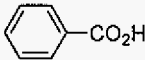
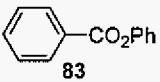
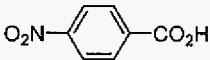
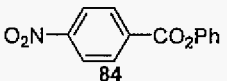
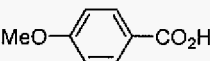
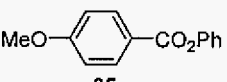
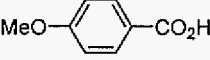
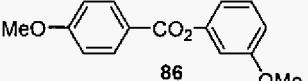
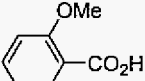
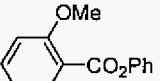
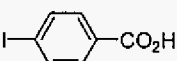
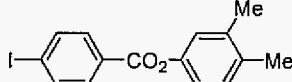
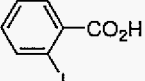
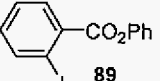
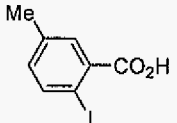
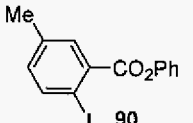
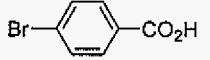
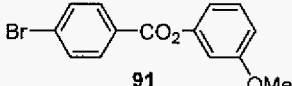
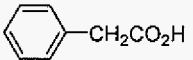
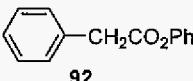
^a All reactions were run under the following reaction conditions, unless otherwise specified: 0.25 mmol of the phenol and the indicated amount of silylaryl triflate and CsF were stirred in 4 mL of MeCN at room temperature.

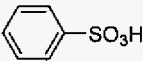
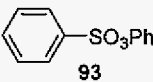
^b When 1.1 equiv of the strong base DBU were added, the yield did not improve.

***O*-Arylation of Carboxylic Acids.**

The *O*-arylation of carboxylic acids has also been investigated as a method to generate aryl esters. One needs to use 2.0 equiv of silylaryl triflate plus 4.0 equiv of CsF in the reaction with carboxylic acids in order to obtain good yields of the corresponding *O*-arylation products. The results are summarized in Table 5. As shown in Table 5, benzoic acid and a number of functionally-substituted benzoic acids react smoothly with silylaryl triflates **1a**, **1b** and **1c** to generate the corresponding aryl esters in high yields. Benzoic acids with an electron-donating group, like a methoxy group (Table 5, entries 4-6), generally afford better yields than benzoic acids with an electron-withdrawing group, like a nitro group (Table 5, entry 2). Halogen-substituted carboxylic acids also work well with silylaryl triflates **1a**, **1b** and **1c** to afford good yields of aryl esters, even when a bulky iodo group is present in the *ortho* position (Table 5, entries 7-10). Unfortunately, aliphatic carboxylic acids do not react well with silylaryl triflates and CsF under our reaction conditions. For example, phenylacetic acid reacts with 2.0 equiv of silylaryl triflate **1a** and 4.0 equiv of CsF to afford only a 45% yield of the corresponding aryl ester (Table 5, entry 11). The reason for the low yields of aryl esters from aliphatic carboxylic acids is not clear at this time. When benzenesulfonic acid was employed to react with silylaryl triflate **1a**, only a 33% yield of phenyl benzenesulfonate was obtained (Table 5, entry 12).

Table 5. Facile *O*-Arylation of Carboxylic Acids^a

entry	carboxylic acid	silylaryl triflate (equiv)	CsF (equiv)	time (h)	product	% isolated yield
1		1a (2.0)	4.0	24	 83	81
2		1a (2.0)	4.0	24	 84	66
4		1a (2.0)	4.0	24	 85	96
5		1b (2.0)	4.0	24	 86	98
6		1a (2.0)	4.0	24	 87	84
7		1c (2.0)	4.0	24	 88	81
8		1a (2.0)	4.0	24	 89	75
9		1a (2.0)	4.0	24	 90	89
10		1b (2.0)	4.0	24	 91	89
11		1a (2.0)	4.0	24	 92	45

12		1a (2.0)	4.0	24		33
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^a All reactions were run under the following reaction conditions, unless otherwise specified: 0.25 mmol of the carboxylic acid and the indicated amount of silylaryl triflate and CsF were stirred in 4 mL of MeCN at room temperature.

Conclusions

We have developed an efficient, mild, transition metal-free method for the *N*-arylation of amines, sulfonamides, and carbamates, and *O*-arylation of phenols and aromatic carboxylic acids. The regioselectivity of the methoxy-substituted silylaryl triflate **1b** is excellent. With other silylaryl triflates, such as **1d** and **1e**, two isomers are obtained. Mono-arylated and diarylated amines can easily be obtained from primary amines by simply controlling the ratio of the reactants. A variety of functional groups are compatible with the reaction conditions, including nitro, hydroxyl, aldehyde, ketone, ester and amide groups, as well as double bonds and triple bonds. We have also shown that halides, which are not compatible with Pd-mediated arylation procedures, readily tolerate our reaction conditions. This chemistry nicely complements classical methods for the *N*-arylation of amines and sulfonamides, and the *O*-arylation of phenols and carboxylic acids.

Experimental Section

General

The ¹H and ¹³C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F) and visualization was

effected with short wavelength UV light (254 nm) and basic KMnO_4 solution [3 g of KMnO_4 + 20 g of K_2CO_3 + 5 ml of NaOH (5 %) + 300 ml of H_2O]. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. All yields reported in the publication represent an average of at least two independent runs. CsF and acetonitrile were purchased from Sigma-aldrich Co.. The product characterization data, and ^1H and ^{13}C NMR spectra for compounds **1**, **2**, **9**, **14**, **21**, **22**, **32**, **35**, **36**, **37**, **38**, **44**, **46**, **48**, and **53** have been reported in our previous communication.^{22a} The product characterization data, and ^1H and ^{13}C NMR spectra for compounds **62**, **63**, **64**, **67**, **68**, **69**, **70**, **71**, **75**, **76**, **83**, **84**, **85**, **86**, **89**, and **91** have been reported in our previous communication.^{22b}

General Procedure for the Mono *N*-Arylation of Aromatic Amines (Table 1). To a solution of MeCN (4 mL), aromatic amine (0.25 mmol) and silylaryl triflate (0.275 mmol) was added CsF (0.4 mmol). The reaction mixture was allowed to stir at room temperature and monitored by TLC to establish completion of the reaction. The resulting solution was washed with brine (20 mL) and extracted with diethyl ether (20 mL). The combined ether fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product.

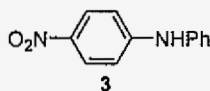
General Procedure for the Mono *N*-Arylation of Alkylamines (Table 2). To a solution of MeCN (4 mL), alkylamine (0.25 mmol) and silylaryl triflate (0.225 mmol) was added CsF (0.4 mmol). The reaction mixture was allowed to stir at room temperature and monitored by TLC to establish completion of the reaction. The resulting solution was washed with brine (20 mL) and extracted with diethyl ether (20 mL). The combined ether fractions were dried

over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product.

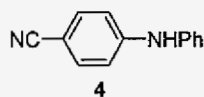
General Procedure for the Diarylation of Amines and Sulfonamides (Tables 1-3). To a solution of MeCN (4 mL), the amine or sulfonamide (0.25 mmol) and silylaryl triflate (0.6 mmol) was added CsF (1.2 mmol). The reaction mixture was allowed to stir at room temperature for 3 d for *N*-arylated amines and 1 d for *N*-arylated sulfonamides. The resulting solution was washed with brine (20 mL) and extracted with diethyl ether (20 mL). The combined ether fractions were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product.

General Procedure for the *O*-Arylation of Phenols (Table 4). To a solution of MeCN (4 mL), the phenol (0.25 mmol) and the silylaryl triflate (0.375 mmol) was added CsF (0.75 mmol). The reaction mixture was allowed to stir at room temperature for 1 d and the resulting solution was washed with brine (20 mL) and extracted with diethyl ether (20 mL). The combined ether fractions were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product.

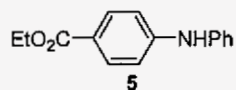
General Procedure for the *O*-Arylation of Carboxylic Acids (Table 5). To a solution of MeCN (4 mL), the carboxylic acid (0.25 mmol) and the silylaryl triflate (0.5 mmol) was added CsF (1.0 mmol). The reaction mixture was allowed to stir at room temperature for 1 d and the resulting solution was washed with brine (20 mL) and extracted with diethyl ether (20 mL). The combined ether fractions were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product.

Characterization data:

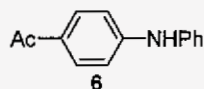
***N*-(4-Nitrophenyl)aniline (3).** The indicated compound was obtained in an 85% yield as a light yellow solid: mp 135-136 °C (lit.³² 134-135 °C); the ¹H and ¹³C NMR spectra match the literature data.³³



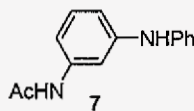
4-(Phenylamino)benzonitrile (4). The indicated compound was obtained in a 90% yield as a white solid: mp 99-100 °C (lit.³⁴ 101-102 °C); the ¹H and ¹³C NMR spectra match the literature data.³³



Ethyl 4-(phenylamino)benzoate (5). The indicated compound was obtained in a 92% yield as light yellow oil. The ¹H and ¹³C NMR spectra match the literature data.³⁵

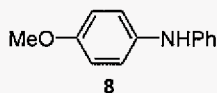


***N*-(4-Acetylphenyl)aniline (6).** The indicated compound was obtained in a 94% yield as a light yellow solid: mp 105-106 °C (lit.³⁶ 104-105 °C); the ¹H and ¹³C NMR spectra match the literature data.³⁷

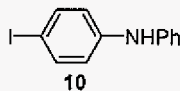


***N*-[3-(Phenylamino)phenyl]acetamide (7).** The indicated compound was obtained in a 95% yield as a light yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 2.04 (s, 3H), 5.79 (s, 1H),

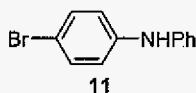
6.77 (dd, $J = 8.1, 1.5$ Hz, 1H), 6.88 (t, $J = 7.2$ Hz, 1H), 6.94-7.01 (m, 3H), 7.09 (t, $J = 7.8$ Hz, 1H), 7.19 (t, $J = 7.8$ Hz, 2H), 7.29 (t, $J = 1.8$ Hz, 1H), 8.15 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 24.7, 109.4, 112.6, 113.2, 118.6, 121.5, 129.6, 129.9, 139.4, 142.9, 144.3, 169.5; HRMS m/z 226.1109 (calcd $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$, 226.1106).



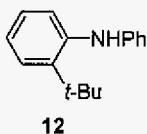
***N*-(4-Methoxyphenyl)aniline (8).** The indicated compound was obtained in an 89% yield as a white solid: mp 101-102 °C (lit.³⁸ 102-103 °C); the ^1H and ^{13}C NMR spectra match the literature data.³⁷



***N*-Phenyl-4-iodoaniline (10).** The indicated compound was obtained in a 92% yield as a light yellow solid: mp 100-102 °C (lit.³⁹ 102-104 °C); the ^1H and ^{13}C NMR spectra match the literature data.³⁹

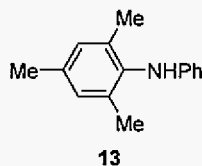


***N*-Phenyl-4-bromoaniline (11).** The indicated compound was obtained in a 91% yield as a light yellow solid: mp 87-89 °C (lit.³⁶ 87-89 °C); the ^1H and ^{13}C NMR spectra match the literature data.⁴⁰

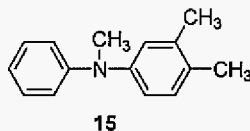


***N*-Phenyl-2-*tert*-butylaniline (12).** The indicated compound was obtained in a 77% yield as a yellow solid: mp 64-65 °C; ^1H NMR (300 MHz, CDCl_3) δ 1.46 (s, 9H), 5.42 (s, 1H), 6.82-

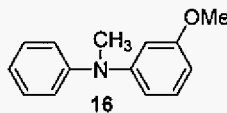
6.86 (m, 3H), 7.09-7.47 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 30.8, 35.1, 116.2, 119.4, 124.2, 126.2, 127.1, 127.3, 129.5, 141.4, 143.6, 146.2; IR (CDCl_3 , cm^{-1}) 3454, 3047, 2962, 2097, 2870, 1595, 1497; HRMS m/z 225.1520 (calcd $\text{C}_{16}\text{H}_{19}\text{N}$, 225.1517).



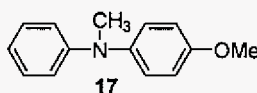
***N*-Phenyl-2,4,6-trimethylaniline (13).** The indicated compound was obtained in a 90% yield as a yellow solid: mp 54-56 °C (lit.⁴¹ 56 °C); the ^1H and ^{13}C NMR spectra match the literature data.⁴¹



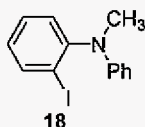
***N*-Methyl-*N*-phenyl-3,4-dimethylaniline (15).** The indicated compound was obtained in a 97% yield as a yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 2.75 (s, 3H), 2.28 (s, 3H), 3.33 (s, 3H), 6.87-6.98 (m, 5H), 7.12 (d, $J = 8.1$ Hz, 1H), 7.24-7.30 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 19.4, 20.3, 40.6, 118.1, 119.8, 120.6, 124.5, 129.2, 130.7, 131.3, 137.8, 147.2, 149.7; IR (CDCl_3 , cm^{-1}) 3021, 2920, 2863, 1595, 1497; HRMS m/z 211.1364 (calcd $\text{C}_{15}\text{H}_{17}\text{N}$, 211.1361).



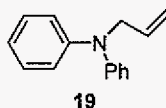
***N*-Methyl-*N*-phenyl-3-methoxyaniline (16).** The indicated compound was obtained in a 47% yield as a yellow oil; the ^1H and ^{13}C NMR spectra match the literature data.⁴²



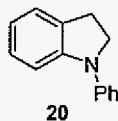
***N*-Methyl-*N*-phenyl-4-methoxyaniline (17).** The indicated compound was obtained in a 47% yield as a yellow oil; the ^1H and ^{13}C NMR spectra match the literature data.⁴²



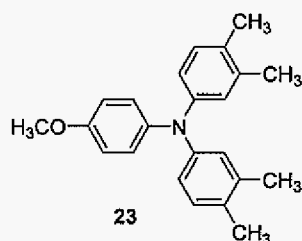
***N*-Methyl-*N*-phenyl-2-iodoaniline (18).** The indicated compound was obtained in a 97% yield as a white solid: mp 31-33 °C; ^1H NMR (300 MHz, CDCl_3) δ 3.20 (s, 3H), 6.54 (d, J = 8.8 Hz, 2H), 6.75 (t, J = 7.2 Hz, 1H), 6.95-7.00 (m, 3H), 7.35 (t, J = 7.2 Hz, 1H), 7.94 (d, J = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 39.3, 101.4, 113.6, 117.9, 128.3, 129.1, 129.9, 130.2, 140.5, 148.7, 150.7; IR (CDCl_3 , cm^{-1}) 3054, 3035, 2918, 2881, 2811, 1609, 1497; HRMS m/z 309.0019 (calcd $\text{C}_{13}\text{H}_{12}\text{IN}$, 309.0014).



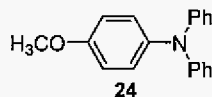
***N*-Allyl-*N*-phenylaniline (19).** The indicated compound was obtained in a 97% yield as a yellow oil; the ^1H and ^{13}C NMR spectra match the literature data.⁴³



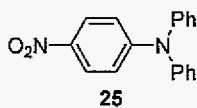
1-Phenylindoline (20). The indicated compound was obtained in a 97% yield as a yellow oil; the ^1H and ^{13}C NMR spectra match the literature data.⁴³



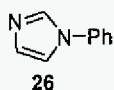
***N*-(3,4-Dimethylphenyl)-*N*-(4-methoxyphenyl)-3,4-dimethylaniline (23).** The indicated compound was obtained in a 93% yield as a white solid: mp 110-111 °C; ^1H NMR (300 MHz, CDCl_3) δ 2.14 (s, 6H), 2.19 (s, 6H), 6.74-6.82 (m, 6H), 6.95-7.03 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 19.3, 20.2, 55.7, 114.8, 120.9, 124.7, 126.6, 130.2, 130.4, 137.4, 141.7, 146.5, 155.7; IR (CDCl_3 , cm^{-1}) 3017, 2963, 2932, 2918, 2858, 1606, 1501; HRMS m/z 331.1942 (calcd $\text{C}_{23}\text{H}_{25}\text{NO}$, 331.1936).



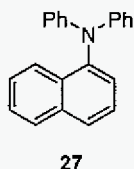
***N,N*-Diphenyl-4-methoxyaniline (24).** The indicated compound was obtained in a 90% yield as a yellow solid: mp 98-100 °C (lit.⁴⁴ 98-100 °C); the ^1H and ^{13}C NMR spectra match the literature data.⁴⁵



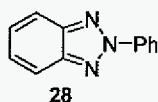
***N,N*-Diphenyl-4-nitroaniline (25).** The indicated compound was obtained in a 55% yield as a yellow solid: mp 139-141 °C (lit.⁴⁶ 138-139 °C); the ^1H and ^{13}C NMR spectra match the literature data.⁴⁷



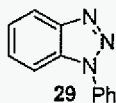
1-Phenyl-1*H*-imidazole (26). The indicated compound was obtained in a 76% yield as a yellow oil; the ^1H and ^{13}C NMR spectra match the literature data.⁴⁸



***N,N*-Diphenylnaphthalen-1-amine (27).** The indicated compound was obtained in an 81% yield as a white solid: mp 135-137 °C (lit.⁴⁴ 136-137 °C); the ^1H and ^{13}C NMR spectra match the literature data.⁴⁴

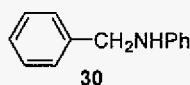


2-Phenyl-2*H*-benzo[*d*][1,2,3]triazole (28). The indicated compound was obtained in a 20% yield as a white solid: mp 109-110 °C (lit.⁴⁹ 108-110 °C); ^1H NMR (300 MHz, CDCl_3) δ 7.40-7.49 (m, 3H), 7.54-7.60 (m, 2H), 7.92-7.96 (m, 2H), 8.36 (dd, $J = 9.0, 1.2$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 118.6, 120.8, 127.4, 129.2, 129.6, 140.6, 145.2.

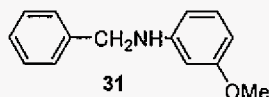


1-Phenyl-1*H*-benzo[*d*][1,2,3]triazole (29). The indicated compound was obtained in a 72% yield as a white solid: mp 85-86 °C (lit.⁵⁰ 85-87 °C); the ^1H and ^{13}C NMR spectra match the literature data.⁵¹

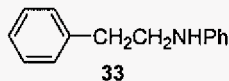
35



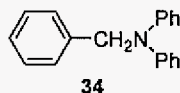
***N*-Benzylaniline (30).** The indicated compound was obtained in a 70% yield as a yellow oil; the ^1H NMR spectrum matches the literature data.⁵²



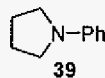
***N*-Benzyl-3-methoxyaniline (31).** The indicated compound was obtained in a 71% yield as a yellow oil; the ^1H and ^{13}C NMR spectra match the literature data.⁵³



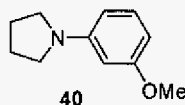
***N*-(2-Phenylethyl)aniline (33).** The indicated compound was obtained in a 66 % yield as a yellow oil; the ^1H and ^{13}C NMR spectra match the literature data.⁵⁴



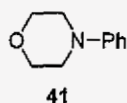
***N,N*-Diphenylaniline (34).** The indicated compound was obtained in a 97% yield as a yellow solid: mp 86-87 °C (lit.²⁷ 88-89 °C); the ^1H and ^{13}C NMR spectra match the literature data.⁵⁵



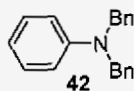
1-Phenylpyrrolidine (39). The indicated compound was obtained in a 95% yield as a yellow oil; the ^1H and ^{13}C NMR spectra match the literature data.⁵⁶



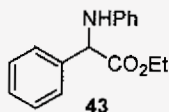
***N*-(3-Methoxyphenyl)pyrrolidine (40).** The indicated compound was obtained in a 97% yield as a yellow oil; the ^1H and ^{13}C NMR spectra match the literature data.⁵⁷



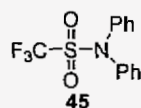
4-Phenylmorpholine (41). The indicated compound was obtained in an 81% yield as a yellow oil; the ^1H and ^{13}C NMR spectra match the literature data.⁵⁸



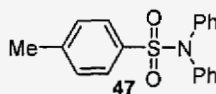
***N,N*-Dibenzylaniline (42).** The indicated compound was obtained in a 99% yield as a yellow oil; The ^1H and ^{13}C NMR spectra match the literature data.⁵⁹



***N*-Phenylphenylalanine ethyl ester (43).** The indicated compound was obtained in a 65% yield as a colorless oil; The ^1H and ^{13}C NMR spectra match the literature data.⁶⁰

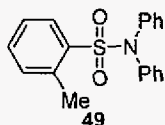


***N,N*-Diphenyltrifluoromethanesulfonamide (45).** The indicated compound was obtained in a 78% yield as a white solid: mp 105-106 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 7.33-7.49 (m, 10H); ^{13}C NMR (75 MHz, CDCl_3) δ 120.6 (q, $J = 322$ Hz), 128.6, 129.1, 130.0, 140.1; IR (CDCl_3 , cm^{-1}) 3087, 3071, 3017, 1589, 1492; HRMS m/z 301.0388 (calcd $\text{C}_{13}\text{H}_{10}\text{F}_3\text{NO}_2\text{S}$, 301.0384).

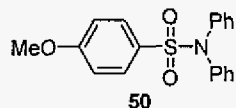


***N,N*-Diphenyl-4-methylbenzenesulfonamide (47).** The indicated compound was obtained in a 100% yield as a yellow solid: mp 138-139 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 2.43 (s,

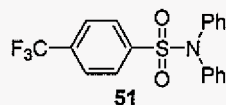
3H), 7.25-7.32 (m, 12H), 7.60 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 21.8, 127.6, 128.0, 128.6, 129.5, 129.8, 137.8, 141.8, 143.8; IR (CDCl_3 , cm^{-1}) 3098, 3067, 2922, 1592, 1345; HRMS m/z 323.0986 (calcd $\text{C}_{19}\text{H}_{17}\text{NO}_2\text{S}$, 323.0980).



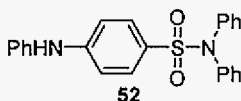
***N,N*-Diphenyl-2-methylbenzenesulfonamide (49).** The indicated compound was obtained in a 99% yield as a yellow solid: mp 65-67 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 2.51 (s, 3H), 7.20-7.33 (m, 12H), 7.44 (td, $J = 7.2$, 0.9 Hz, 1H), 7.83 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 21.0, 126.3, 127.7, 128.8, 129.5, 130.9, 132.8, 133.3, 138.4, 138.5, 141.7; IR (CDCl_3 , cm^{-1}) 3062, 3037, 2933, 1589, 1487; HRMS m/z 323.0986 (calcd $\text{C}_{19}\text{H}_{17}\text{NO}_2\text{S}$, 323.0980).



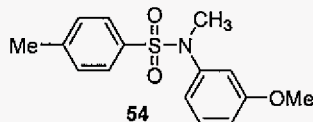
***N,N*-Diphenyl-4-methoxybenzenesulfonamide (50).** The indicated compound was obtained in a 100% yield as a yellow solid: mp 122-123 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 3.86 (s, 3H), 6.93 (dd, $J = 6.9$, 2.1 Hz, 2H), 7.22-7.34 (m, 10H), 7.32 (dd, $J = 6.9$, 2.1 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.8, 114.3, 127.6, 128.6, 129.5, 130.1, 132.4, 141.8, 163.2; IR (CDCl_3 , cm^{-1}) 3076, 3006, 2985, 2945, 2844, 1594, 1493; HRMS m/z 339.0934 (calcd $\text{C}_{19}\text{H}_{17}\text{NO}_3\text{S}$, 339.0929).



***N,N*-Diphenyl-4-(trifluoromethyl)benzenesulfonamide (51).** The indicated compound was obtained in a 91% yield as a white solid: mp 128-129 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 7.24-7.37 (m, 10H), 7.75 (d, $J = 8.7$ Hz, 2H), 7.82 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 123.5 (q, $J = 271.4$ Hz), 126.3 (q, $J = 3.7$ Hz), 128.2, 128.4, 128.6, 129.7, 134.7 (q, $J = 32.9$ Hz), 141.2, 144.2 (q, $J = 1.3$ Hz); IR (CDCl_3 , cm^{-1}) 3063, 2919, 1587, 1490; HRMS m/z 337.0700 (calcd $\text{C}_{19}\text{H}_{14}\text{F}_3\text{NO}_2\text{S}$, 337.0697).

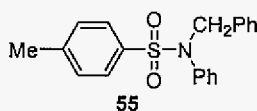


***N,N*-Diphenyl-4-(phenylamino)benzenesulfonamide (52).** The indicated compound was obtained in a 75% yield as a pale yellow solid: mp 206-208 °C; ^1H NMR (acetone- d_6 , 300 MHz) δ 7.03-7.17 (m, 3H), 7.25-7.39 (m, 14H), 7.54 (dt, $J = 9.0, 2.7$ Hz, 2H), 8.11 (s, 1H); ^{13}C NMR (75 MHz, acetone- d_6) δ 114.2, 120.6, 123.0, 127.3, 128.6, 129.3, 129.5, 129.6, 129.9, 141.3, 142.3, 149.0; IR (CDCl_3 , cm^{-1}) 3367, 3055, 3034, 1743, 1591, 1145; HRMS m/z 400.1252 (calcd $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$, 400.1245).

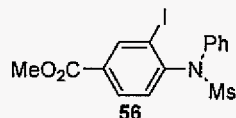


***N*-(3-Methoxyphenyl)-*N*-methyl-4-methylbenzenesulfonamide (54).** The indicated compound was obtained in a 91% yield as a colorless oil; ^1H NMR (CDCl_3 , 300 MHz) δ 2.41 (s, 3H), 3.14 (s, 3H), 3.76 (s, 3H), 6.61-6.64 (m, 1H), 6.71 (t, $J = 2.4$ Hz, 1H), 6.79-6.82 (m, 1H), 7.18 (t, $J = 8.4$ Hz, 1H), 7.24 (d, $J = 8.1$ Hz, 2H), 7.46 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 21.8, 38.4, 55.6, 112.9, 113.3, 118.6, 128.1, 129.5, 133.7, 143.0, 143.8,

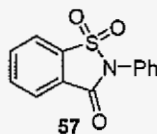
160.0; IR (CDCl₃, cm⁻¹) 3058, 3027, 2932, 1589, 1485; HRMS m/z 291.0932 (calcd C₁₅H₁₆NO₃S, 291.0929).



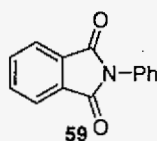
***N*-Benzyl-*N*-phenyl-4-methylbenzenesulfonamide (55).** The indicated compound was obtained in a 94% yield as a yellow solid: mp 139-140 °C; ¹H NMR (CDCl₃, 400 MHz) δ 2.44 (s, 3H), 4.74 (s, 2H), 6.98-7.01 (m, 2H), 7.18-7.29 (m, 10H), 7.55 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 21.9, 54.9, 127.8, 127.9, 128.0, 128.6, 128.7, 129.1, 129.2, 129.7, 135.7, 136.2, 139.2, 143.8; IR (CDCl₃, cm⁻¹) 3062, 3027, 2918, 1595, 1491; HRMS m/z 337.1140 (calcd C₂₀H₁₉NO₂S, 337.1136).



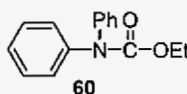
Methyl 3-iodo-4-(*N*-phenylmethanesulfonylamino)benzoate (56). The indicated compound was obtained in a 98% yield as a pale yellow solid: mp 135-137 °C; ¹H NMR (CDCl₃, 400 MHz) δ 3.27 (s, 3H), 3.92 (s, 3H), 7.25-7.27 (m, 1H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 8.10 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.58 (d, *J* = 2.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 41.7, 52.9, 101.7, 126.0, 127.1, 129.6, 130.7, 131.8, 132.0, 140.0, 146.5, 164.9; IR (CDCl₃, cm⁻¹) 3065, 3026, 2952, 2930, 2849, 2256, 1724, 1351; HRMS m/z 430.9693 (calcd C₁₅H₁₄INO₄S, 430.9688).



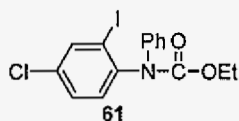
***N*-Phenylsaccharin (57).** The indicated compound was obtained in a 72% yield as a white solid: mp 187-189 °C (lit.⁶¹ 189-191 °C); the ¹H and ¹³C NMR spectra match the literature data.⁶¹



***N*-Phenylphthalimide (59).** The indicated compound was obtained in a 60% yield as a white solid: mp 207-209 °C (lit.⁶² 207.9-209.9 °C); the ¹H and ¹³C NMR spectra match the literature data.⁶³

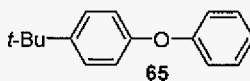


Ethyl *N,N*-diphenylcarbamate (60). The indicated compound was obtained in a 96% yield as a white solid: mp 69-70 °C (lit.⁶⁴ 69-70 °C); the ¹H NMR spectrum matches the literature data.⁶⁴

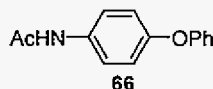


Ethyl *N*-(4-chloro-2-iodophenyl)-*N*-phenylcarbamate (61). The indicated compound was obtained in a 93% yield as a colorless oil; ¹H NMR (CDCl₃, 300 MHz) δ 1.25 (t, *J* = 7.2 Hz, 3H), 4.21-4.26 (m, 2H), 7.13-7.19 (m, 2H), 7.25-7.35 (m, 5H), 7.90 (d, *J* = 2.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 14.8, 62.8, 100.9, 125.2, 125.8, 128.9, 129.8, 130.7, 133.9, 139.5,

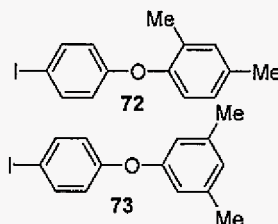
141.5, 143.6, 153.9; IR (CDCl₃, cm⁻¹) 3065, 2980, 2932, 2906, 1721, 1493, 1308; HRMS *m/z* 440.9684 (calcd C₁₅H₁₃ClINO₂, 440.9679).



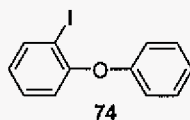
(4-*tert*-Butylphenyl) phenyl ether (65). The indicated compound was obtained in an 85% yield as a colorless oil; the ¹H and ¹³C NMR spectra match the literature data.⁶⁵



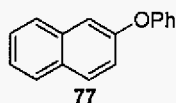
***N*-(4-Phenoxyphenyl)acetamide (66).** The indicated compound was obtained in a 91% yield as a white solid: mp 130-131°C (lit.⁶⁶ 128-129 °C); the ¹H and ¹³C NMR spectra match the literature data.⁶⁷



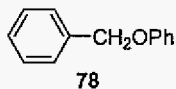
2,4-Dimethylphenyl 4-iodophenyl ether (72) and 3,5-dimethylphenyl 4-iodophenyl ether (73). The indicated compounds were obtained as a 1:1.5 mixture in a 92% yield as a colorless oil; ¹H NMR (CDCl₃, 300 MHz) δ 2.18 (s, 3H), 2.32 (s, 8H), 2.35 (s, 3H), 6.66-6.69 (m, 5H), 6.76-6.80 (m, 4H), 6.85 (d, *J* = 8.1 Hz, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 7.09 (s, 1H), 7.55-7.65 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 16.3, 21.1, 21.6, 84.6, 85.9, 117.1, 119.1, 120.6, 121.1, 125.8, 128.1, 130.2, 132.5, 134.5, 138.7, 138.8, 140.0, 151.5, 156.7, 157.9, 158.7.



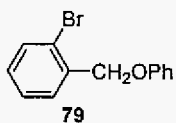
2-Iodophenyl phenyl ether (74). The indicated compound was obtained in a 90% yield as a pale yellow solid: mp 52-54 °C (lit.⁶⁸ 53-54 °C); the ¹H and ¹³C NMR spectra match the literature data.⁶⁸



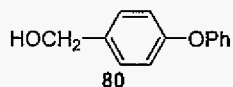
2-Naphthyl phenyl ether (77). The indicated compound was obtained in an 84% yield as a pale yellow solid: mp 46-47 °C (lit.⁶⁹ 45-46 °C); ¹H NMR (CDCl₃, 300 MHz) δ 7.07 (d, J = 7.8 Hz, 2H), 7.14 (t, J = 7.5 Hz, 1H), 7.24-7.47 (m, 6H), 7.69 (d, J = 7.8 Hz, 1H), 7.80-7.84 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 114.3, 119.4, 120.2, 123.7, 124.9, 126.7, 127.4, 127.9, 130.0, 130.1, 130.4, 134.5, 155.3, 157.4.



Benzyl phenyl ether (78). The indicated compound was obtained in a 25% yield as a colorless oil; the ¹H and ¹³C NMR spectra match the literature data.⁷⁰

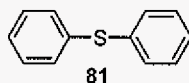


2-Bromobenzyl phenyl ether (79). The indicated compound was obtained in a 36% yield as a pale yellow solid: mp 35-37 °C (lit.⁷¹ 34-36 °C); the ¹H and ¹³C NMR spectra match the literature data.⁷²

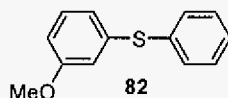


4-Phenoxybenzyl alcohol (80). The indicated compound was obtained in a 36% yield as a white solid: mp 54-55 °C (lit.⁷³ 54.5 °C); ¹H NMR (CDCl₃, 300 MHz) δ 1.93 (s, 1H), 4.64 (s,

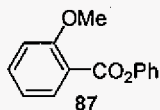
2H), 7.00 (dd, $J = 9.0, 2.1$ Hz, 4H), 7.09 (t, $J = 7.2$ Hz, 1H), 7.30-7.35 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 65.1, 119.1, 119.2, 123.5, 128.9, 130.0, 135.9, 157.0, 157.4; IR (CDCl_3 , cm^{-1}) 3385, 063, 3053, 2949, 2887, 1591, 1491; HRMS m/z 200.0840 (calcd $\text{C}_{13}\text{H}_{12}\text{O}_2$, 200.0836).



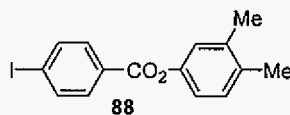
Diphenyl sulfide (81). The indicated compound was obtained in a 70% yield as a colorless oil; the ^1H and ^{13}C NMR spectra match the literature data.⁷⁴



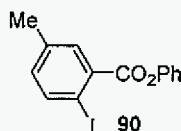
3-Methoxyphenyl phenyl sulfide (82). The indicated compound was obtained in a 66% yield as a colorless oil; ^1H NMR (CDCl_3 , 300 MHz) δ 3.74 (s, 3H), 6.74-6.78 (m, 1H), 6.85-6.92 (m, 2H), 7.17-7.38 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.5, 113.0, 116.1, 123.2, 127.5, 129.5, 130.2, 131.7, 135.5, 137.5, 160.3; IR (CDCl_3 , cm^{-1}) 3059, 3002, 2957, 2935, 2833, 1588, 1476; HRMS m/z 216.0611 (calcd $\text{C}_{13}\text{H}_{12}\text{OS}$, 216.0608).



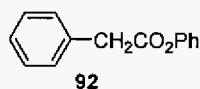
Phenyl 2-methoxybenzoate (87). The indicated compound was obtained in an 84% yield as a pale yellow solid: mp 54-56 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 3.92 (s, 3H), 7.01-7.06 (m, 2H), 7.20-7.27 (m, 3H), 7.38-7.56 (m, 3H), 8.00 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 56.3, 112.5, 120.4, 122.1, 125.9, 129.6, 132.4, 134.5, 151.2, 160.1, 164.6; IR (CDCl_3 , cm^{-1}) 3071, 2963, 2941, 2839, 1743, 1487; HRMS m/z 228.0789 (calcd $\text{C}_{14}\text{H}_{12}\text{O}_3$, 228.0786).



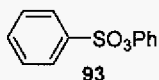
3,4-Dimethylphenyl 4-iodobenzoate (88). The indicated compound was obtained in an 81% yield as a pale yellow solid: mp 79-80 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 2.28 (s, 3H), 2.29 (s, 3H), 6.93 (dd, $J = 6.1, 2.4$ Hz, 1H), 6.99 (d, $J = 2.4$ Hz, 1H), 7.18 (d, $J = 8.1$ Hz, 1H), 7.85-7.93 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 19.5, 20.2, 101.7, 118.8, 122.7, 129.5, 130.7, 131.7, 134.6, 138.1, 138.3, 148.9, 165.3; IR (CDCl_3 , cm^{-1}) 3085, 2970, 2935, 1728; HRMS m/z 351.9965 (calcd $\text{C}_{15}\text{H}_{13}\text{IO}_2$, 351.9960).



Phenyl 2-iodo-5-methylbenzoate (90). The indicated compound was obtained in an 89% yield as a yellow oil; ^1H NMR (CDCl_3 , 300 MHz) δ 2.37 (s, 3H), 7.01-7.05 (m, 1H), 7.24-7.29 (m, 3H), 7.40-7.45 (m, 2H), 7.83 (d, $J = 1.8$ Hz, 1H), 7.91 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 21.1, 90.7, 121.8, 126.3, 129.7, 132.5, 134.5, 138.5, 141.6, 151.0, 165.3; IR (CDCl_3 , cm^{-1}) 3059, 3042, 2952, 2921, 2854, 1742, 1591; HRMS m/z 337.9808 (calcd $\text{C}_{14}\text{H}_{11}\text{IO}_2$, 337.9803).



Phenyl phenylacetate (92). The indicated compound was obtained in a 45% yield as a white solid: mp 39-40 °C (lit.⁷⁵ 40-41.5 °C); the ^1H NMR spectrum matches the literature data.⁷⁵



Phenyl benzenesulfonate (93). The indicated compound was obtained in a 33 % yield as a colorless oil: ^{13}C NMR (75 MHz, CDCl_3) δ 120.7, 122.6, 127.4, 128.7, 129.3, 129.8, 134.4, 149.8. The ^1H NMR spectrum matches the literature data.⁷⁶

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CHAPTER 2. Synthesis of Carbazoles and Dibenzofurans via Cross-Coupling of *o*-Iodoanilines and *o*-Iodophenols with Silylaryl Triflates and Subsequent Pd-Catalyzed Cyclization

Based on a full paper submitted to *Tetrahedron*⁵⁰

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Abstract

An efficient route to a variety of carbazoles and dibenzofurans has been developed. It involves the reaction of *o*-iodoanilines or *o*-iodophenols with silylaryl triflates in the presence of CsF to afford the *N*- or *O*-arylated products, which are subsequently cyclized using a Pd catalyst to carbazoles and dibenzofurans in good to excellent yields. By using this methodology, the carbazole alkaloid mukonine has been synthesized in 76% overall yield in three steps.

Introduction

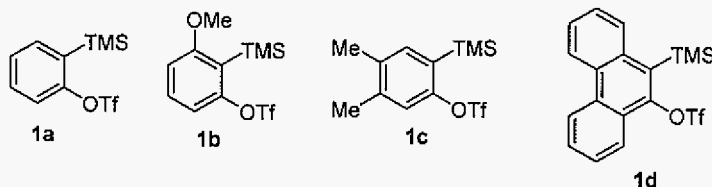
Carbazoles¹ and dibenzofurans² are important heteroaromatic compounds, which display a wide variety of biological activities. Substituted carbazoles have attracted considerable attention because carbazole alkaloids are a growing class of natural products, which show antioxidative and biological activities, such as antitumor, anti-inflammatory and antibiotic activities.^{1a,3} Carbazole derivatives are also widely used as building blocks for potential electroluminescent materials,⁴ polymers with useful electrical and thermal properties,⁵ and

host materials for triplet emitters in organic light-emitting diodes.⁶ The dibenzofuran-containing phytoalexins show manifold biological activities eliciting a strong interest from chemists and biologists.⁷ Dibenzofurans have been shown to be potent, selective ECE inhibitors.⁸

Considerable effort has been devoted to the development of efficient methods for the construction of the carbazole ring system,^{3a,9} for example, the classical Fisher-Borsche synthesis,¹⁰ and cyclization via indole Diels-Alder reactions.¹¹ Recently, transition-metal catalysts have been widely used to synthesize the carbazole and dibenzofuran ring systems.^{3b,3d,12} Quite recently, Wu has utilized anionic cycloaromatization to synthesize 5-substituted dibenzofurans and carbazoles.¹³

While there are presently a number of useful synthetic procedures to prepare these compounds, there remain several limitations as well. (1) Most of the present procedures involve several steps and the overall yields usually are not very good. (2) The starting materials are often not very readily available.⁹ (3) Harsh reaction conditions are usually needed. One simple, new, efficient and general method to synthesize both the carbazole and dibenzofuran ring systems would be quite attractive, because of the growing interest in these compounds.¹⁴

In the last twenty years, considerable work has been reported on the synthesis of indoles and benzofurans by the cross-coupling of *o*-haloanilines or *o*-halophenols with alkynes by palladium annulation chemistry.¹⁵ However, no one has reported the cross-coupling of *o*-haloanilines or *o*-halophenols with arynes or their synthetic equivalents, which, if successful, could afford one of the most direct routes to carbazoles and dibenzofurans. Recently, silylaryl triflate **1a**¹⁶ has been employed to generate benzyne,



which readily undergoes a variety of electrophilic and nucleophilic reactions,¹⁷ several novel insertion reactions,¹⁸ and Pd-catalyzed annulation reactions.¹⁹ More recently, we have reported a simple, economical, and efficient one-pot, two-step procedure to synthesize the carbazole and dibenzofuran ring systems in good to excellent yields through the cross-coupling of *o*-iodoanilines or *o*-iodophenols with silylaryl triflates, followed by palladium-catalyzed intramolecular cyclization.²⁰ Herein, we wish to provide a full account of the scope and limitations of this chemistry. We have also applied this chemistry to the synthesis of an interesting carbazole alkaloid, mukonine, in high yield.

Results and Discussion

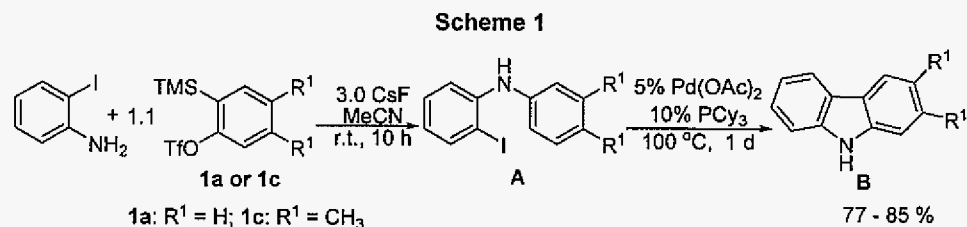
Preparation of the Aryne Precursors.

The arynes **1a-d** were selected as substrates for our experiments. Aryne precursor **1a** was selected as the simplest and most readily available aryne to study the scope of this chemistry, since it is commercially available. Aryne precursor **1b** was selected to study the regioselectivity of the palladium-catalyzed cyclization step. The synthesis of silylaryl triflates **1a**,²¹ **1b**,²² **1c**,²³ and **1d**²⁴ have previously been reported.

Synthesis of Carbazoles and Analogues.

The essential elements of our approach to the carbazole ring system are shown in Scheme 1. *o*-Iodoaniline is first allowed to react with the silylaryl triflate under very mild reaction conditions to afford the *N*-arylated *o*-iodoanilines **A**,^{17c} which subsequently undergo intramolecular palladium-catalyzed arylation in the same pot to produce the carbazole

derivatives **B** in good yields.



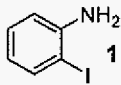
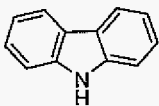
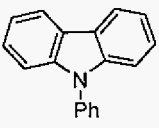
Our initial studies were directed towards achieving the optimal reaction conditions for the palladium-catalyzed intramolecular arylation step (**A**→**B**) (Scheme 1). A range of palladium catalysts was employed. We found that Pd(OAc)₂ was the best catalyst. All other palladium catalysts [PdCl₂(PPh₃)₂, Pd(PPh₃)₄, Pd(dba)₂] examined afforded either comparable or lower yields. The ligand added to the reaction did not make much difference. Thus, the ligands dppe, dppm, and PCy₃ all worked well in our system. However, the solvent had a big effect on this cross-coupling reaction; DMF and toluene both gave very low yields of the carbazole products, while MeCN proved to be the best solvent for this process. The first step in this sequence had already been optimized during some of our earlier work on the *N*-arylation of amines.^{17c} After our optimization work was complete, we settled on the following standard two step procedure. The iodoaniline (0.25 mmol), the silylaryl triflate (1.1 equiv) and CsF (3.0 equiv) were allowed to react at room temperature for 10 h in acetonitrile (4.0 mL) under air. Then Pd(OAc)₂ (3.1 mg, 5 mol %) and PCy₃ (Cy = cyclohexyl, 7.0 mg, 10 mol %) were added and the reaction heated to 100 °C for 1 d under argon.

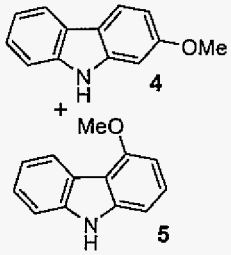
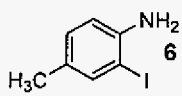
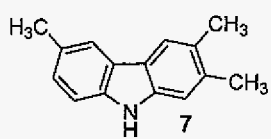
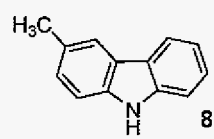
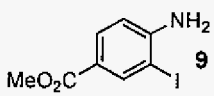
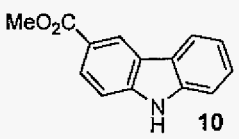
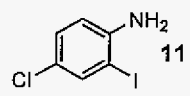
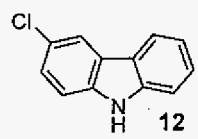
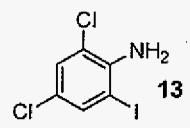
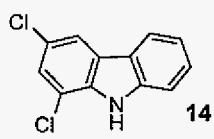
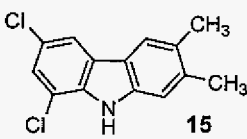
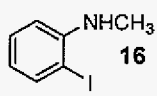
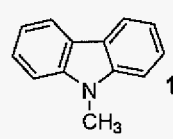
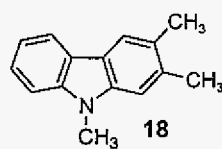
We next studied the scope and limitations of this two-step cross-coupling process by allowing a wide variety of iodoanilines and their derivatives to react with the silylaryl triflates **1a-d**. The results are summarized in Table 1. A variety of *o*-iodoanilines react with silylaryl triflates **1a**, **1b** or **1c** to afford, after Pd-catalyzed cyclization, high yields of the

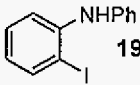
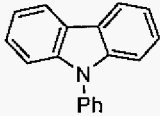
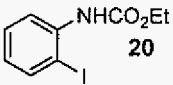
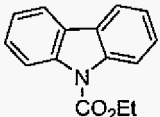
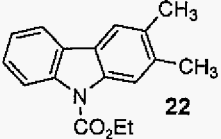
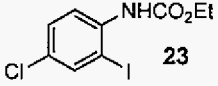
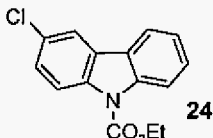
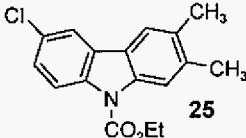
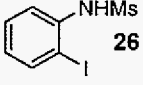
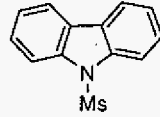
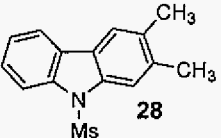
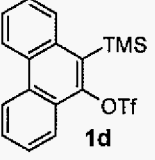
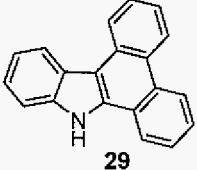
desired carbazoles (Table 1, entries 1-9). When a slight excess (1.1 equiv) of the silylaryl triflate **1a** was allowed to react with *o*-iodoaniline (entry 1), the desired carbazole was obtained in a 77% yield under our standard reaction conditions. Where 2.4 equiv of the silylaryl triflate **1a** were allowed to react with *o*-iodoaniline, the *N*-phenylcarbazole was isolated in only a 66% yield (entry 2). *o*-Iodoaniline also reacts with the methoxy-substituted silylaryl triflate **1b**, followed by palladium-catalyzed cyclization, to afford two carbazole derivatives **4** and **5** in a 5:1 ratio (entry 3). The fact that carbazole **4** is the major product can be easily explained by a steric effect during the Pd-catalyzed cyclization. The Pd-catalyzed cyclization is occurring at the less hindered position away from the methyl group. When silylaryl triflate **1c** was employed with 2-iodo-4-methylaniline, we obtained the desired product in a 68% yield (entry 4). Approximately a 4% yield of the isomeric product 1,2,6-trimethylcarbazole was also observed as detected by GC/MS. Again the Pd-catalyzed cyclization is occurring with high regioselectivity for the less hindered position away from the methyl group. When substituted iodoanilines were allowed to react with silylaryl triflate **1a**, the corresponding carbazole derivatives could be obtained in good to excellent yields (entries 5-8). Similarly, 2,4-dichloro-6-iodoaniline reacts with 1.1 equiv of silylaryl triflate **1c** to afford the desired product in an 85% yield. Approximately a 5% yield of the isomeric product 6,8-dichloro-1,2-dimethylcarbazole was also observed as detected by GC/MS (entry 9). The presence of a chlorine in the starting anilines does not appear to interfere with the overall process (entries 7-9). *N*-Methylcarbazole is also readily obtained in an 82% yield when *N*-methyl-2-iodoaniline was employed as the substrate (entry 10). *N*-Phenylcarbazole was obtained in a slightly higher yield by this cross-coupling procedure, when *N*-phenyl-2-iodoaniline was employed, instead of 2-iodoaniline and an excess of aryne (compare entries 2

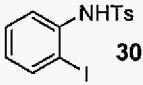
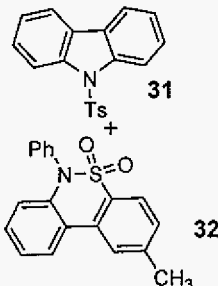
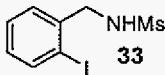
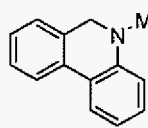
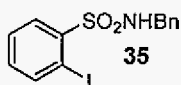

and 12). *N*-(2-Iodophenyl)methanesulfonamide and ethyl 2-iodophenylcarbamate and their derivatives also react well with the silylaryl triflate **1a** or **1c** to afford high yields of the corresponding products (entries 13-18); again, only about 5% of a product isomeric with the products shown in entries 16 and 18 was observed by GC/MS analysis. Interestingly, when silylaryl triflate **1d** was allowed to react with *N*-(2-iodophenyl)methanesulfonamide, we did not obtain the expected product, but rather the deprotected dibenzo[*a,c*]carbazole in a 62% yield (entry 19). Apparently the extended π -conjugation of the dibenzo[*a,c*]carbazole facilitates loss of the methanesulfonyl group. It is interesting that the reaction of *N*-tosyl-2-iodoaniline and silylaryl triflate **1a** afforded a 1:1 ratio of compounds **31** and **32** in an 83% overall yield (entry 20). It seems rather surprising that the Pd-catalyzed cyclization onto the tosyl group competes so effectively with cyclization onto the phenyl ring. One can also start with *N*-(2-iodobenzyl)methanesulfonamide or *N*-benzyl-2-iodobenzenesulfonamide and silylaryl triflate **1a** and produce the corresponding six membered ring products in good yields (entries 21 and 22). None of the product from cyclization onto the benzyl group in entry 22 is observed, possibly because this would involve formation of a seven membered ring.

Table 1. Synthesis of Carbazoles and Analogues^a

entry	substrate	aryl triflate	CsF (equiv)	product	% isolated yield
1		1a	3.0		77
2	1	1a	5.0		66 ^b

3	1	1b	3.0	 4 + 5	61 (5:1)
4	 6	1c	3.0	 7	68
5	6	1a	3.0	 8	69
6	 9	1a	3.0	 10	68
7	 11	1a	3.0	 12	72
8	 13	1a	3.0	 14	87
9	13	1c	3.0	 15	85
10	 16	1a	3.0	 17	82
11	16	1c	3.0	 18	71

12		1a	3.0		3	76 ^c
13		1a	3.0		21	85
14	20	1c	3.0		22	85
15		1a	3.0		24	86
16	23	1c	3.0		25	85
17		1a	3.0		27	85
18	26	1c	3.0		28	85
19	26		3.0		29	62

20		1a	3.0		83 (1:1)
21		1a	3.0		66
22		1a	3.0		62

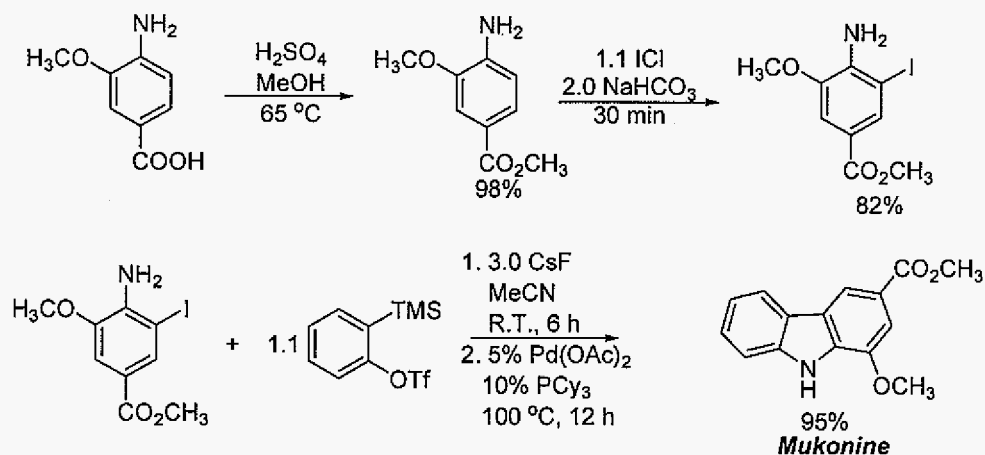
^a Reaction conditions: 0.25 mmol of aryl iodide are allowed to react with 1.1 equiv of the aryl triflate and the number of equiv of CsF shown in the table in 4.0 mL of MeCN as the solvent at room temperature for 10 h, followed by the addition of 5 mol % Pd(OAc)₂ and 10 mol % PCy₃ and heating for 1 d at 100 °C. ^b 2.4 Equiv of aryl triflate were employed and the reaction was run at room temperature for 2 d, followed by the addition of 5 mol % Pd(OAc)₂ and 10 mol % PCy₃ and heating for 1 d at 100 °C. ^c The reaction was run at room temperature for 1.5 d, followed by the addition of 5 mol % Pd(OAc)₂ and 10 mol % PCy₃ and heating for 1 d at 100 °C.

Synthesis of Mukonine.

Mukonine [1-methoxy-3-(methoxycarbonyl)carbazole] is an alkaloid obtained from the Indian curry-leaf tree (*Murraya koenigii*).²⁵ Mukonine has been synthesized by several different methods.^{3,26} By employing our procedure, mukonine can be obtained in a 76% overall yield in three steps from commercially available 4-amino-3-methoxybenzoic acid (Scheme 2). 3-Methoxy-4-aminobenzoic acid reacts with methanol to afford methyl 3-

methoxy-4-aminobenzoate in a 98% yield. Iodination using ICl in dichloromethane affords methyl 4-amino-3-iodo-5-methoxybenzoate in an 82% yield. Employing our standard reaction conditions on methyl 4-amino-3-iodo-5-methoxybenzoate, mukonine can be obtained in a 95% yield in only one additional step.

Scheme 2



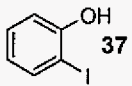
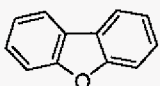
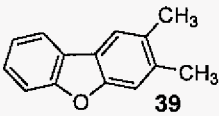
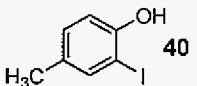
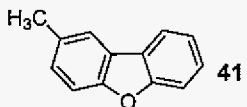
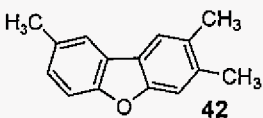
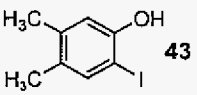
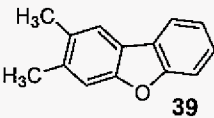
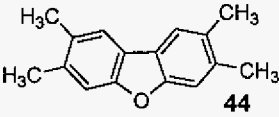
76% overall yield for three steps

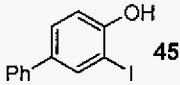
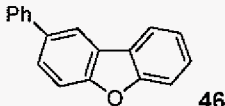
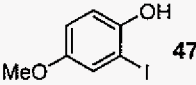
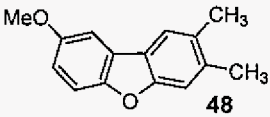
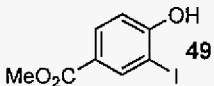
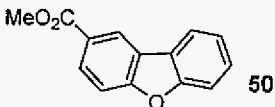
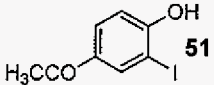
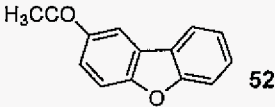
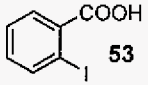
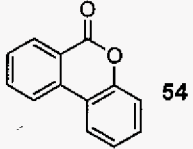
Synthesis of Dibenzofurans and Analogues.

Since some effort has been devoted to the synthesis of carbazoles and related compounds, it seemed natural for us to extend this chemistry to the synthesis of dibenzofurans and related compounds by using *o*-iodophenol and derivatives. Indeed, we have also investigated the use of *o*-iodophenols in this process. Here, we needed to use 1.2 equiv of silylaryl triflates **1a** or **1c**, and 3.5 equiv of CsF to get the yields specified. The results are summarized in Table 2. *o*-Iodophenol reacts with silylaryl triflate **1a** or **1c** to afford, after Pd-catalyzed cyclization, the corresponding dibenzofurans in 70% and 67% yields respectively (entries 1 and 2). A variety of substituted iodophenols have also been employed in this process; most of them work quite well and afford the desired compounds in modest to good yields (entries 3-10). Similar to our carbazole results, when silylaryl triflate **1c** was used in this cross-coupling

process, approximately a 4-5% yields of the expected isomeric products were observed as detected by GC/MS (entries 2, 4-6, and 8). It is noteworthy that the presence of an electron-withdrawing ester or ketone moiety on the phenol presents no difficulties and, in fact, these substrates gave slightly higher yields of the desired products (entries 9 and 10). In this process, one can also start with 2-iodobenzoic acid and allow it to react with silylaryl triflate **1a**. Cyclization produces the desired six membered ring product benzo[*c*]coumarin in a 46% yield (entry 11).

Table 2. Synthesis of Dibenzofurans and Analogues^a

entry	substrate	aryl triflate	CsF (equiv)	product	% isolated yield
1	 37	1a	3.5	 38	70
2	37	1c	3.5	 39	67 ^b
3	 40	1a	3.5	 41	68
4	40	1c	3.5	 42	68 ^b
5	 43	1a	3.5	 39	63
6	43	1c	3.5	 44	61 ^b

7		45	1a	3.5		46	63
8		47	1c	3.5		48	77 ^{b,c}
9		49	1a	3.5		50	80
10		51	1a	3.5		52	76
11		53	1a	4.0		54	46 ^d

^a Reaction conditions: 0.25 mmol of aryl iodide are allowed to react with 1.2 equiv of aryl triflate and the number of equiv of CsF shown in the table in 4.0 mL of MeCN as the solvent at room temperature for 10 h, followed by the addition of 5 mol % Pd(OAc)₂ and 10 mol % PCy₃ and heating for 1 d at 100 °C. ^b About 4% of the isomeric product was detected by GC/MS. ^c In this reaction, 10 mol % Pd(OAc)₂ and 20 mol % PCy₃ were used. ^d 1.5 Equiv of aryl triflate were used.

Conclusions

In summary, we have developed a simple and efficient one-pot, two-step procedure to synthesize the carbazole and dibenzofuran ring systems and related compounds. It involves the reaction of *o*-iodoanilines or *o*-iodophenols with silylaryl triflates in the presence of CsF to afford the *N*- or *O*-arylated products, which are subsequently cyclized using a Pd catalyst to carbazoles and dibenzofurans. The starting materials are commercially available or can be

easily prepared using known chemistry. The yields are good to excellent. Several new and multisubstituted carbazoles and dibenzofurans have been synthesized using this chemistry. By using this methodology, the carbazole alkaloid mukonine has been synthesized in 76% overall yield in three steps from a commercially available starting material.

Experimental Section

General.

The ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. All yields reported represent an average of at least two independent runs. Silylaryl triflate **1a** is commercially available. The substituted silylaryl triflates (**1b**,²⁷ **1c**,²⁸ and **1d**²⁹) were prepared according to literature procedures. The product characterization data, and ^1H and ^{13}C NMR spectra for compounds **2**, **14**, **15**, **17**, **21**, **22**, **27**, **33**, **34**, **38**, and **50** have been reported in our previous communication.²⁰

Preparation of the starting materials: The starting materials **1**, **6**, **9**, **11**, **13**, **26**, **30**, **35**, **37**, **43**, **45**, **49**, and **53** are commercially available; the starting materials **16**,³¹ **19**,³² **20**,³³ **23**,³³ **40**,³⁴ **47**,³⁵ and **51**³⁶ are easily prepared by literature procedures from commercially available starting materials.

Methyl 4-amino-3-iodo-5-methoxybenzoate. To a solution of 0.905 g of methyl 4-amino-3-methoxybenzoate (5 mmol) and 0.84 g of NaHCO_3 (10 mmol) in 15 mL of CH_2Cl_2 at room temperature was added 0.893 g of ICl (5.5 mmol) in 5 mL of CH_2Cl_2 . The reaction mixture was stirred at room temperature for 30 min. The resulting solution was washed with

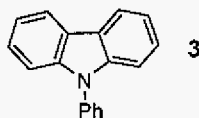
saturated NaHCO_3 (20 mL) solution and extracted with CH_2Cl_2 (20 mL). The combined CH_2Cl_2 fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford 1.25 g of the desired product (82% yield) as a white solid: mp 93-94 °C; ^1H NMR (300 MHz, CDCl_3) δ 3.86 (s, 3H), 3.89 (s, 3H), 4.69 (s, 2H), 7.39 (d, $J = 1.8$ Hz, 1H), 8.00 (d, $J = 1.8$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 52.2, 56.2, 80.7, 110.7, 120.5, 133.3, 142.0, 145.3, 166.3; IR (CDCl_3 , cm^{-1}) 3495, 3391, 3001, 2949, 2838, 1694, 1268; HRMS m/z 306.9701 (calcd $\text{C}_9\text{H}_{10}\text{INO}_3$, 306.9705).

General Procedure for the Synthesis of Carbazoles and Related Compounds (Table 1).

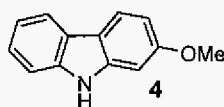
In a 4 dram vial, the silylaryl triflate (0.275 mmol) and CsF (0.75 mmol) were added to a solution of the *o*-iodoaniline (0.25 mmol) in acetonitrile (4 mL). The reaction mixture was allowed to stir at room temperature for 10 h under air. The vial was then flushed with argon and $\text{Pd}(\text{OAc})_2$ (5 mol %, 3.1 mg) and PCy_3 (10 mol %, 7.0 mg) were added to the reaction, which was heated to 100 °C for 1 d. The resulting solution was washed with brine (20 mL) and extracted with diethyl ether (20 mL). The combined ether fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product.

General Procedure for the Synthesis of Dibenzofurans and Related Compounds (Table 2).

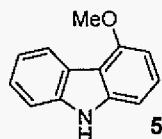
In a 4 dram vial, the silylaryl triflate (0.3 mmol) and CsF (0.875 mmol) were added to a solution of the *o*-iodophenol (0.25 mmol) in acetonitrile (4 mL). The rest of the procedure is the same as that used in the synthesis of the carbazoles.

Characterization Data:

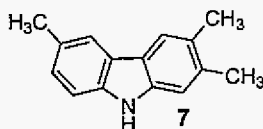
N-Phenylcarbazole (3). The indicated compound was obtained in a 66% yield as a white solid: mp 91-93 °C (lit.³⁷ 89-90 °C); the ¹H and ¹³C NMR spectra match the literature data.³⁸



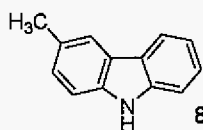
2-Methoxycarbazole (4). The indicated compound was obtained in a 51% yield as a white solid: mp 233-235 °C; the ¹H and ¹³C NMR spectra match the literature data;³⁹ HRMS m/z 197.0843 (calcd C₁₃H₁₁NO, 197.0840).



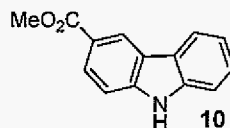
4-Methoxycarbazole (5). The indicated compound was obtained in a 10% yield as a white solid: mp 133-135 °C (lit.³⁹ 135 °C); the ¹H NMR spectrum matches the literature data;⁴⁰ ¹³C NMR (75 MHz, acetone-d₆) δ 55.6, 100.6, 103.7, 110.1, 112.8, 119.8, 122.8, 123.3, 125.1, 126.9, 138.8, 141.1, 156.5; HRMS m/z 197.0843 (calcd C₁₃H₁₁NO, 197.0840).



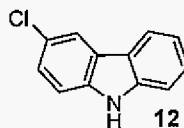
2,3,6-Trimethylcarbazole (7). The indicated compound was obtained in a 68% yield as a white solid: mp 208-209 °C (lit.⁴¹ 211-211.5 °C); ¹H NMR (300 MHz, acetone-d₆) δ 2.38 (s, 6H), 2.47 (s, 3H), 7.15 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.25 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.81 (s, 1H), 9.89 (s, 1H); ¹³C NMR (75 MHz, acetone-d₆) δ 19.4, 29.1, 20.8, 110.6, 111.6, 119.7, 120.5, 121.4, 123.5, 126.3, 126.9, 127.5, 134.4, 138.6, 139.6; IR (CDCl₃, cm⁻¹) 3393, 2963, 2934, 2852, 1464; HRMS *m/z* 209.1209 (calcd C₁₅H₁₅N, 209.1204).



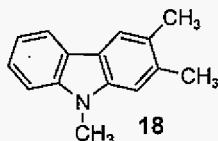
3-Methylcarbazole (8). The indicated compound was obtained in a 69% yield as a light yellow solid: mp 205-207 °C (lit.⁴² 205-206 °C); the ¹H and ¹³C NMR spectra match the literature data.⁴²



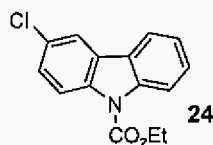
Methyl carbazole-3-carboxylate (10). The indicated compound was obtained in a 68% yield as a white solid: mp 171-173 °C (lit.⁴³ 168-170 °C); the ¹H and ¹³C NMR spectra match the literature data.⁴³



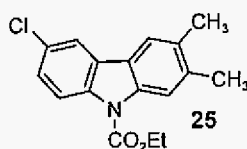
3-Chlorocarbazole (12). The indicated compound was obtained in a 72% yield as a light yellow solid: mp 199-200 °C (lit.⁴⁴ 198-200 °C); the ¹H and ¹³C NMR spectra match the literature data.³⁷



2,3,9-Trimethylcarbazole (18). The indicated compound was obtained in a 71% yield as a light yellow solid: mp 88-89 °C; ^1H NMR (300 MHz, acetone- d_6) δ 2.43 (s, 3H), 2.46 (s, 3H), 3.78 (s, 3H), 7.15-7.23 (m, 2H), 7.33 (d, J = 8.1 Hz, 1H), 7.41 (td, J = 6.9, 0.9 Hz, 1H), 7.83 (s, 1H), 8.02 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, acetone- d_6) δ 19.3, 20.3, 38.3, 114.6, 115.2, 120.2, 120.9, 124.1, 124.3, 126.5, 127.0, 132.9, 136.9, 137.4, 138.7; IR (CDCl_3 , cm^{-1}) 3016, 2961, 2935, 2899, 1601; HRMS m/z 209.1209 (calcd $\text{C}_{15}\text{H}_{15}\text{N}$, 209.1204).

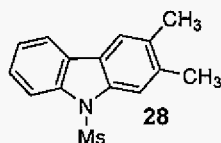


Ethyl 3-chlorocarbazole-9-carboxylate (24). The indicated compound was obtained in an 85% yield as a white solid: mp 102-104 °C; ^1H NMR (300 MHz, CDCl_3) δ 1.54 (t, J = 7.2 Hz, 3H), 4.57 (q, J = 7.2 Hz, 2H), 7.24-7.50 (m, 3H), 7.84-7.88 (m, 2H), 8.18 (d, J = 9.0, 1H), 8.24 (d, J = 9.0, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.7, 63.5, 116.6, 117.5, 119.6, 120.0, 123.7, 124.9, 127.3, 127.4, 128.1, 129.1, 136.8, 138.8, 152.3; IR (CDCl_3 , cm^{-1}) 3128, 3064, 2981, 2919, 1723, 1441; HRMS m/z 273.0560 (calcd $\text{C}_{15}\text{H}_{12}\text{ClNO}_2$, 273.0556).

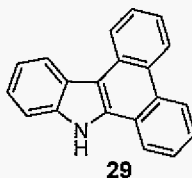


Ethyl 6-chloro-2,3-dimethylcarbazole-9-carboxylate (25). The indicated compound was obtained in an 85% yield as a yellow solid: mp 125-126 °C; ^1H NMR (300 MHz, CDCl_3) δ

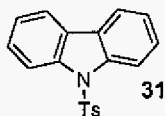
1.54 (t, $J = 7.2$ Hz, 3H), 2.37 (s, 3H), 2.40 (s, 3H), 4.56 (q, $J = 7.2$ Hz, 2H), 7.33 (dd, $J = 8.7$, 2.1 Hz, 1H), 7.59 (s, 1H), 7.80 (d, $J = 2.1$ Hz, 1H), 8.02 (s, 1H), 8.13 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.7, 20.2, 21.2, 63.4, 117.2, 117.5, 119.2, 120.4, 122.9, 126.5, 127.6, 128.9, 132.4, 136.7, 137.3, 137.6, 152.4; IR (CDCl_3 , cm^{-1}) 2980, 2920, 2860, 1727, 1476; HRMS m/z 301.0873 (calcd $\text{C}_{17}\text{H}_{16}\text{ClNO}_2$, 301.0869).



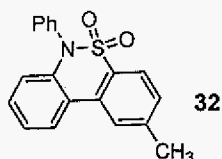
2,3-Dimethyl-9-(methanesulfonyl)carbazole (28). The indicated compound was obtained in an 85% yield as white solid: mp 123-125 $^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 2.41 (s, 3H), 2.43 (s, 3H), 2.93 (s, 3H), 7.38-7.45 (m, 2H), 7.74 (s, 1H), 7.91-7.94 (m, 2H), 8.12 (dd, $J = 7.2$, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.2, 21.1, 38.4, 115.0, 115.5, 120.0, 120.8, 124.3, 124.5, 126.8, 127.1, 133.2, 137.2, 137.3, 138.6; IR (CDCl_3 , cm^{-1}) 3061, 3032, 3012, 2930, 2856, 1471; HRMS m/z 273.0829 (calcd $\text{C}_{15}\text{H}_{15}\text{NO}_2\text{S}$, 273.0823).



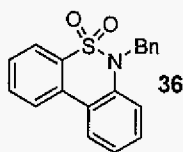
Dibenzo[*a,c*]carbazole (29). The indicated compound was obtained in a 47% yield as a white solid: mp 192-193 $^{\circ}\text{C}$ (lit.⁴⁵ 193-195 $^{\circ}\text{C}$); the ^1H and ^{13}C NMR spectra match the literature data.⁴⁵



9-Tosylcarbazole (31). The indicated compound was obtained in a 41% yield as a white solid: mp 129-130 °C (lit.⁴⁶ 128.5-130 °C); ¹H NMR (300 MHz, CDCl₃) δ 2.34 (s, 3H), 7.22 (dd, $J = 8.7, 0.6$ Hz, 2H), 7.42 (td, $J = 7.5, 0.9$ Hz, 2H), 7.57 (td, $J = 7.5, 1.2$ Hz, 2H), 7.77 (dt, $J = 8.4, 1.8$ Hz, 2H), 8.05-8.08 (m, 2H), 8.36 (dt, $J = 8.4, 0.6$ Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 20.7, 115.2, 120.5, 124.4, 126.6, 126.7, 127.8, 130.1, 134.9, 138.5, 145.8; IR (CDCl₃, cm⁻¹) 3109, 3067, 2902, 1595, 1452; HRMS m/z 321.0827 (calcd C₁₉H₁₅NO₂S, 321.0823).

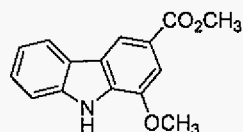


2-Methyl-5,5-dioxide-6-phenyldibenzo[c,e][1,2]thiazine (32). The indicated compound was obtained in a 42% yield as a white solid: mp 208-210 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.55 (s, 3H), 6.98-7.01 (m, 1H), 7.22-7.25 (m, 2H), 7.33-7.40 (m, 6H), 7.83 (s, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 8.03-8.05 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 22.3, 123.4, 123.8, 125.4, 125.5, 125.7, 126.4, 128.3, 128.6, 129.5, 129.7, 132.4, 132.7, 138.4, 140.4, 143.5; IR (CDCl₃, cm⁻¹) 3067, 2925, 2853, 2253, 1600, 1492; HRMS m/z 321.0827 (calcd C₁₉H₁₅NO₂S, 321.0823).

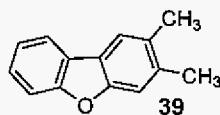


6-Benzyl-5,5-dioxidedibenzo[c,e][1,2]thiazine (36). The indicated compound was obtained in a 62% yield as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 5.05 (s, 2H), 7.18 (s, 5H), 7.23 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.28 (td, $J = 8.0, 1.2$ Hz, 1H), 7.33 (td, $J = 8.0, 1.2$ Hz, 1H), 7.54 (td, $J = 7.6, 1.2$ Hz, 1H), 7.65 (td, $J = 8.0, 1.2$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.93

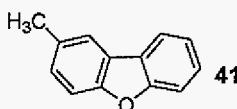
(dd, $J = 7.6, 1.6$ Hz, 1H), 7.99 (dd, $J = 7.6, 1.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 52.9, 122.2, 122.7, 125.6, 125.7, 125.7, 125.8, 127.7, 127.9, 128.4, 128.8, 130.4, 132.5, 132.7, 135.4, 135.9, 138.8; IR (CDCl_3 , cm^{-1}) 3064, 3030, 2923, 2851, 1601, 1477; HRMS m/z 321.0827 (calcd $\text{C}_{19}\text{H}_{15}\text{NO}_2\text{S}$, 321.0823).



Mukonine. The indicated compound was obtained in a 95% yield as a white solid: mp 192-193 °C (lit.⁴⁷ 193-195 °C); the ^1H and ^{13}C NMR spectra match the literature data.⁴⁷

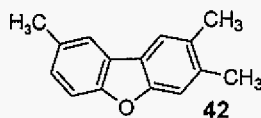


2,3-Dimethyldibenzofuran (39). The indicated compound was obtained in a 67% yield as a white solid: mp 90-91 °C; ^1H NMR (300 MHz, CDCl_3) δ 2.39 (s, 3H), 2.40 (s, 3H), 7.34-7.42 (m, 3H), 7.52 (d, $J = 7.5$ Hz, 1H), 7.68 (s, 1H), 7.87 (dd, $J = 7.5, 0.9$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.2, 20.9, 111.7, 112.4, 120.4, 121.1, 122.1, 122.6, 124.6, 126.6, 131.4, 136.6, 155.3, 156.4; IR (CDCl_3 , cm^{-1}) 3046, 2968, 2941, 2922, 1448; HRMS m/z 196.0890 (calcd $\text{C}_{14}\text{H}_{12}\text{O}$, 196.0888).

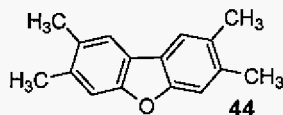


3-Methyldibenzofuran (41). The indicated compound was obtained in a 68% yield as a white solid: mp 42-43 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.49 (s, 3H), 7.22-7.25 (m, 1H), 7.31 (td, $J = 7.6, 1.2$ Hz, 1H), 7.40-7.45 (m, 2H), 7.54 (d, $J = 8.0$ Hz, 1H), 7.73 (t, $J = 0.8$ Hz, 1H), 7.90 (dd, $J = 8.0, 0.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 111.4, 111.9, 120.8,

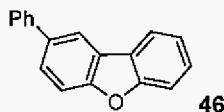
120.9, 122.7, 124.4, 124.5, 127.2, 128.4, 132.4, 154.7, 156.7; IR (CDCl₃, cm⁻¹) 3026, 2978, 2941, 2921, 1446; HRMS m/z 182.0734 (calcd C₁₃H₁₀O, 182.0731).



2,3,6-Trimethyldibenzofuran (42). The indicated compound was obtained in a 68% yield as a white solid: mp 97-98 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.35 (s, 3H), 2.36 (s, 3H), 2.46 (s, 3H), 7.17 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.28 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.61 (s, 1H), 7.63 (d, *J* = 0.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 20.2, 21.0, 21.6, 111.2, 112.4, 120.5, 121.0, 122.1, 124.6, 127.6, 131.2, 132.1, 136.4, 154.7, 155.6; IR (CDCl₃, cm⁻¹) 3014, 2970, 2940, 2921, 1454; HRMS m/z 210.1048 (calcd C₁₅H₁₄O, 210.1044).

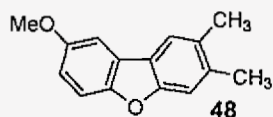


2,3,6,7-Tetramethyldibenzofuran (44). The indicated compound was obtained in a 61% yield as a white solid: mp 183-184 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.40 (s, 6H), 2.41 (s, 6H), 7.32 (s, 2H), 7.64 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 20.2, 20.9, 112.3, 120.8, 122.3, 131.0, 135.7, 155.3; IR (CDCl₃, cm⁻¹) 3026, 2971, 2919, 2856, 1454; HRMS m/z 224.1204 (calcd C₁₆H₁₆O, 224.1201).

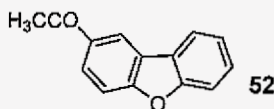


3-Phenyldibenzofuran (46). The indicated compound was obtained in a 63% yield as a white solid: mp 94-96 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.37 (m, 2H), 7.43-7.48 (m, 3H), 7.55-7.66 (m, 5H), 7.96 (dd, *J* = 7.6, 0.8 Hz, 1H), 8.11 (d, *J* = 1.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 112.0, 119.4, 120.9, 123.1, 124.5, 124.9, 126.9, 127.3, 127.6, 127.7,

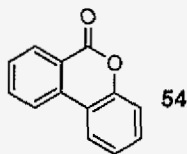
129.1, 136.6, 141.6, 156.0, 156.9; IR (CDCl₃, cm⁻¹) 3057, 3032, 2920, 1601, 1470; HRMS m/z 280.0892 (calcd C₁₈H₁₂O, 280.0888).



2,3-Dimethyl-6-methoxydibenzofuran (48). The indicated compound was obtained in a 67% yield as a white solid: mp 97-98 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.38 (s, 3H), 2.39 (s, 3H), 3.88 (s, 3H), 6.90 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 7.29 (s, 1H), 7.59 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 20.2, 20.8, 55.9, 96.8, 110.7, 112.2, 117.8, 120.4, 120.7, 122.2, 131.3, 135.0, 155.4, 157.7, 159.6; IR (CDCl₃, cm⁻¹) 3015, 2999, 2979, 2939, 1590; HRMS m/z 226.0996 (calcd C₁₅H₁₄O₂, 226.0993).



3-Acetyldibenzofuran (52). The indicated compound was obtained in a 76% yield as a white solid: mp 69-70 °C; ¹H NMR (300 MHz, CDCl₃) δ 2.71 (s, 3H), 7.38 (td, *J* = 7.5, 1.2 Hz, 1H), 7.70 (td, *J* = 7.5, 1.2 Hz, 1H), 7.57 (s, 1H), 7.60 (s, 1H), 7.99 (dd, *J* = 7.5, 0.6 Hz, 1H), 8.10 (dd, *J* = 8.7, 1.8 Hz, 1H), 8.57 (d, *J* = 1.8 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 27.0, 111.8, 112.2, 121.2, 121.8, 123.6, 123.9, 124.8, 128.2, 128.3, 132.7, 157.1, 159.1, 197.5; IR (CDCl₃, cm⁻¹) 3063, 3002, 2922, 2849, 1678, 1598; HRMS m/z 210.0683 (calcd C₁₄H₁₀O₂, 210.0680).



Benzo[c]chromenone (54). The indicated compound was obtained in a 46% yield as a white solid: mp 91-92 °C (lit.⁴⁸ 88-89 °C); the ¹H and ¹³C NMR spectra match the literature data.⁴⁹

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CHAPTER 3. Intermolecular C-N Addition of Amides and S-N Addition of Sulfinamides to Arynes

Based on a communication published in the *Journal of the American Chemical Society*¹⁷

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Abstract

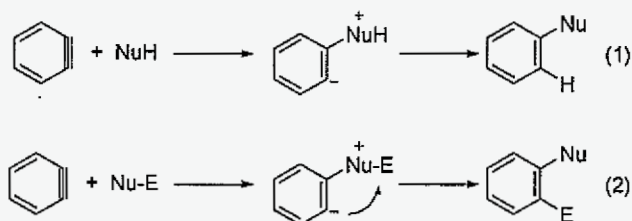
An efficient, mild, transition metal-free method has been developed for the intermolecular C-N σ -bond addition of amides and S-N σ -bond addition of sulfinamides to arynes to form one C-C bond and one heteroatom-carbon bond in one step under very mild reaction conditions. A variety of functional groups are compatible with the reaction conditions. Evidence for a stepwise mechanism is provided.

Introduction

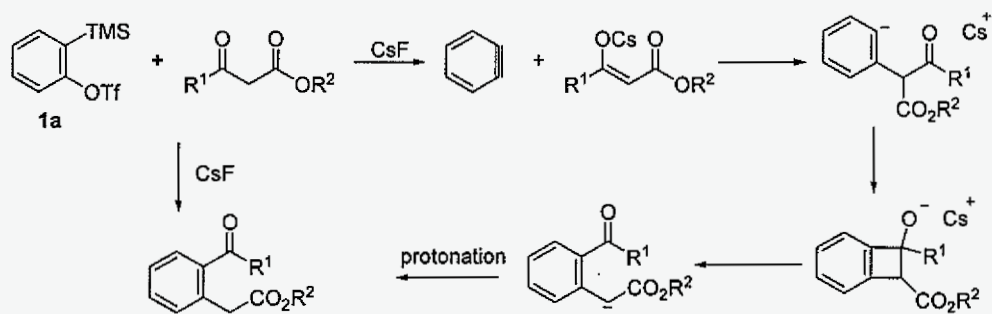
The reaction of arynes with nucleophiles is a unique straightforward method for the synthesis of substituted arenes¹ and the addition of H-X bonds (X = N, O and S) to arynes to construct a new carbon-heteroatom bond is well known.² However, the use of aryne as reagents in synthetic organic chemistry has been somewhat limited, due to the harsh conditions needed to generate arynes and the often uncontrolled reactivity exhibited by these species. Recently, we reported that the N-H bond of amines and sulfonamides,² and the O-H bond of phenols and arenicarboxylic acids³ readily react with arynes generated from silylaryl triflates, such as **1a**, and CsF to afford the corresponding *N*- and *O*-arylation products respectively in excellent yields under mild reaction conditions (Scheme 1, eq. 1). Although

this chemistry has proven useful in organic synthesis, insertion of an aryne into a σ -bond between a nucleophile and an electrophile (Nu-E) should potentially be an even more beneficial process from the standpoint of organic synthesis (Scheme 1, eq. 2). Recently, the palladium-catalyzed insertion of arynes generated from the corresponding silylaryl triflate into Si-Si,⁴ Sn-Sn⁵ and C-Sn⁶ bonds has been reported. While there are examples of the transition-metal free insertion of arynes into C-C (Scheme 2),⁷ S-S⁸ and Te-Te⁹ (Scheme 3) bonds, the number of examples of arynes inserting into polarized heteroatom-containing

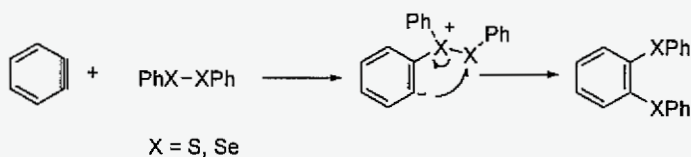
Scheme 1



Scheme 2

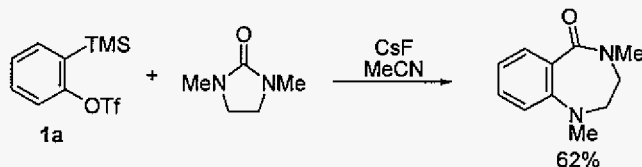


Scheme 3



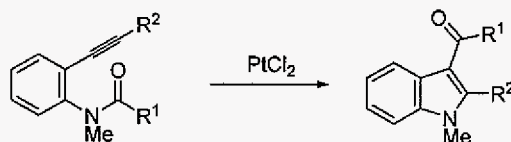
bonds are quite limited. For example, the direct insertion of an aryne into a C-N σ -bond has only been shown to occur with ureas (Scheme 4).¹⁰

Scheme 4



To the best of our knowledge, there is only one example of the intramolecular C-N addition of an amide to an alkyne using a platinum catalyst (Scheme 5).¹¹ Herein, we report a novel, transition metal free, intermolecular C-N addition of amides and S-N addition of sulfinamides to arynes under very mild reaction conditions.

Scheme 5

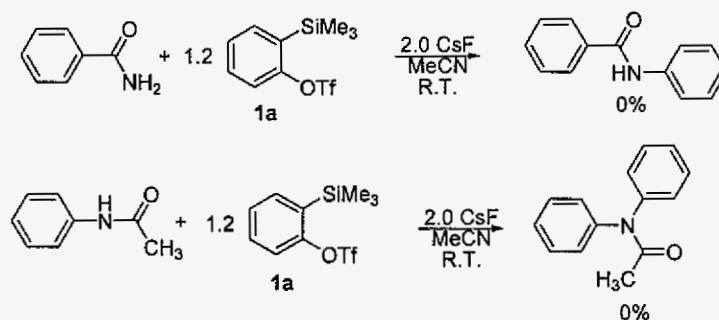


Results and Discussion

Intermolecular C-N Bond Addition of Amides to Arynes.

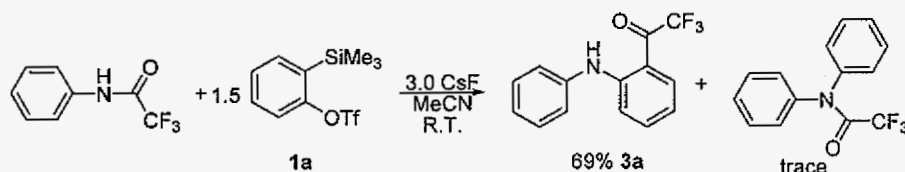
During our work on the *N*-arylation of amines and sulfonamides,² we examined the analogous *N*-arylation chemistry of amides. We first allowed benzamide and *N*-phenylacetamide to react with 1.2 equiv of 2-(trimethylsilyl)phenyl triflate (1a), a known benzyne precursor,¹² and 2.0 equiv of CsF for 1 d (Scheme 6). None of the desired *N*-arylated product was obtained in either of these reactions; only the starting materials were recovered. Simple amides are apparently neither acidic enough to react with the weak base CsF to form the corresponding anion or nucleophilic enough to directly attack the aryne. To prove our hypothesis, *N*-phenyltrifluoroacetamide was employed in this *N*-arylation process. The trifluoromethyl group should increase the acidity of the amide, since it is a strong electron-withdrawing group and might, therefore, be expected to facilitate *N*-arylation.

Scheme 6

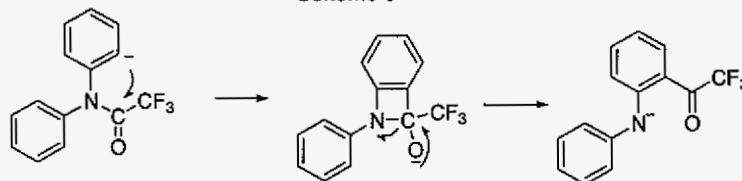


We first allowed *N*-phenyltrifluoroacetamide to react with 1.5 equiv of 2-(trimethylsilyl)phenyl triflate (**1a**) and 3.0 equiv of CsF for 20 h. Surprisingly, only a trace of the *N*-arylated product was detected, while an interesting C-N insertion product 2,2,2-trifluoro-1-[2-(phenylamino)phenyl]ethanone was isolated in a 69% yield (Scheme 7). We believe that this process proceeds through an unstable four-membered ring intermediate, which reopens to generate the trifluoromethyl ketone (Scheme 8). The detailed mechanism of this process will be discussed later.

Scheme 7

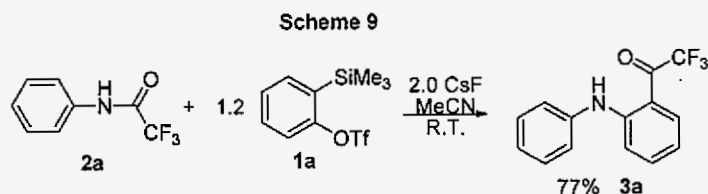


Scheme 8



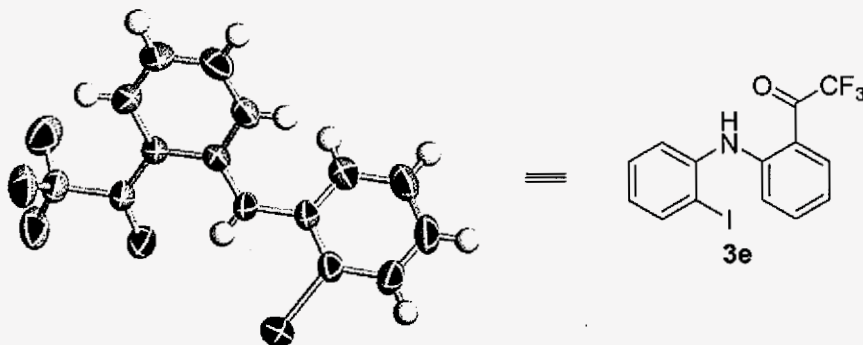
Our initial studies were directed towards achieving the optimal reaction conditions for addition of the C-N σ -bond of amides to the aryne. During this process, we found other solvents, such as THF, dioxane, DMF and toluene, all work inefficiently, and afforded a

lower yield. However, decreasing the amount of the benzyne precursor from 1.5 equiv to 1.2 equiv and also using 2.0 equiv of CsF in MeCN, the desired insertion product can be obtained in a 77% yield at room temperature after only 4 h (Scheme 9).



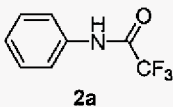
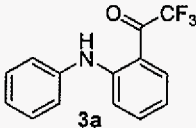
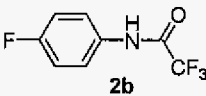
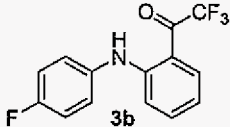
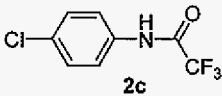
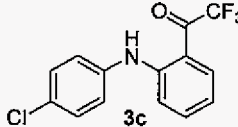
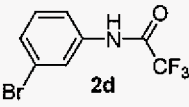
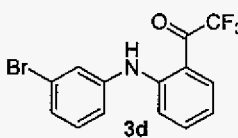

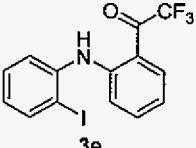
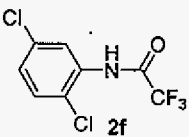
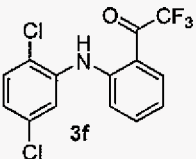
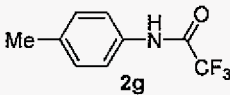
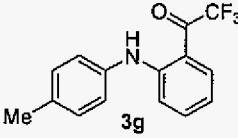
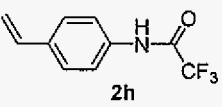
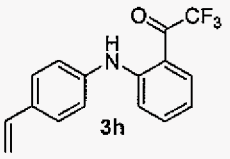
After our optimization work was complete, we settled on the following standard procedure: 0.5 mmol of amide, 1.2 equiv of aryne precursor and 2.0 equiv of CsF in 5.0 mL of MeCN at room temperature for 4 h. We next studied the scope and limitations of this process. A variety of functionally-substituted *N*-aryltrifluoroacetamides and aryne precursors (**1a-f**) was employed in this insertion chemistry. The results are summarized in Table 1. Substrates with different halide groups, such as fluoride, chloride, bromide and iodide, all work very well for this insertion chemistry (entries 1-6). To prove the structure of the insertion product, the x-ray structure of compound **3e** is shown in Figure 1 (entry 5).

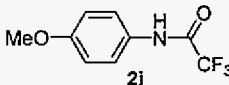
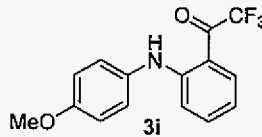
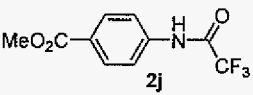
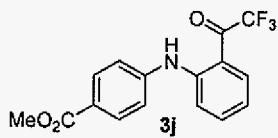
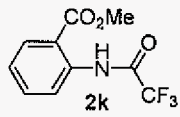
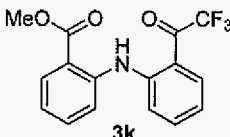
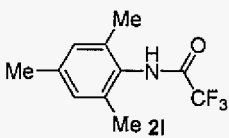
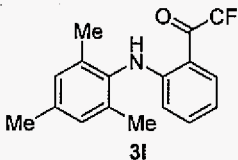
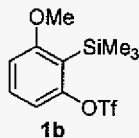
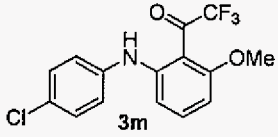
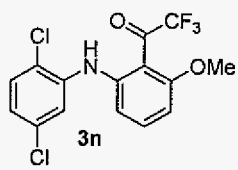
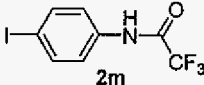
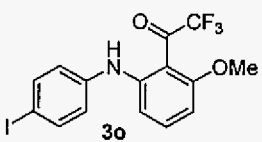
Figure 1. X-Ray Structure for Compound (3e)

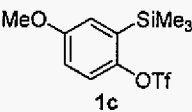
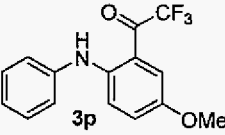
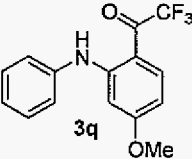
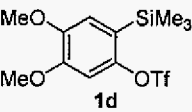
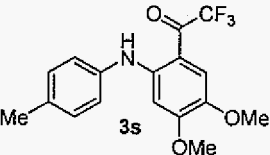
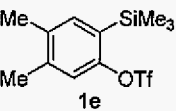
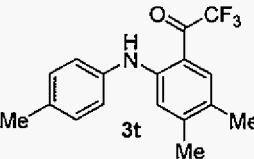
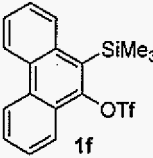
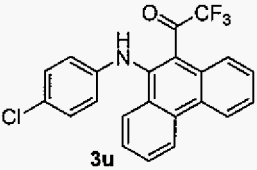
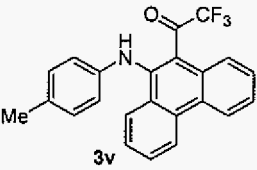
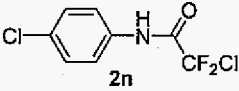
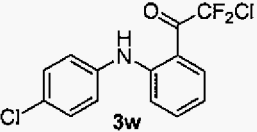
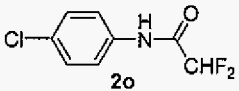
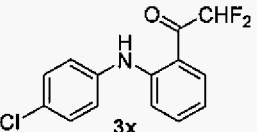


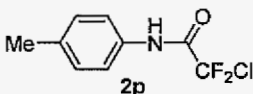
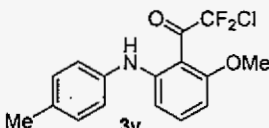
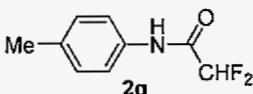
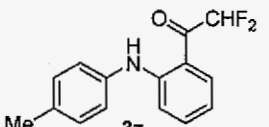
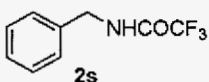
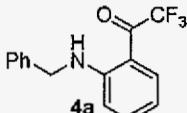
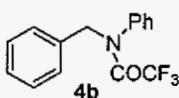
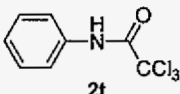
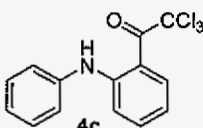
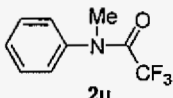
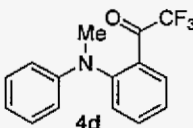
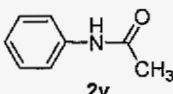
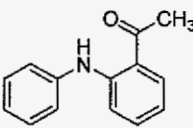
Because the reaction does not involve a transition metal, halides are readily tolerated under our reaction conditions. Substrates with electron-donating and electron-withdrawing groups both work efficiently in this process and afford good yields of the corresponding product (entries 7-11), although substrates with electron-donating groups, such as methoxy and methyl groups, often work a little better than the substrates with electron-withdrawing groups, such as an ester group (compare entries 7, 9 and 10, 11). It is noteworthy that double bonds can be accommodated in this reaction (entry 8). Even the sterically hindered substrate shown in entry 12 affords the corresponding insertion product in a 69% yield. Besides the simple benzyne precursor **1a**, several other aryne precursors (**1b-f**) have also been studied in this chemistry. When the 3-MeO substituted silylaryl triflate **1b** was allowed to react with trifluoroacetamides (**2c**, **2f** and **2m**), excellent yields of the corresponding insertion products were obtained with excellent regioselectivity, since only a single regioisomer was obtained in all three of these cases (entries 13-15). To prove the structure of these insertion products, the x-ray structure of compound **3n** was obtained. It is shown in Figure 2 (entry 14). However, when the 4-MeO substituted silylaryl triflate **1c** was allowed to react with *N*-phenyltrifluoroacetamide (**2a**), two isomers **3p** and **3q** were obtained in a 1:1.1 ratio, which clearly suggests the intermediacy of an aryne in our reaction system (entry 16). The very different regioselectivity observed using these two aryne precursors (**1b** and **1c**) can be readily explained by steric and electronic effects. The use of silylaryl triflate **1b** favors nucleophilic attack at the position *meta* to the methoxy group of the aryne. When using silylaryl triflate **1c**, the steric and electronic effects are very similar in the positions *meta* and *para* to the methoxy group of the aryne. The symmetrical aryne precursors **1d**, **1e** and **1f** also gave good results with a variety of trifluoroacetamides affording good to excellent

Table 1. Addition of C-N Bond of Amides to Arynes.^a

entry	substrate	aryl triflate	product	% yield ^b
1	 2a	1a	 3a	77
2	 2b	1a	 3b	74
3	 2c	1a	 3c	86
4	 2d	1a	 3d	70
5	 2e	1a	 3e	76 ^c
6	 2f	1a	 3f	78
7	 2g	1a	 3g	75
8	 2h	1a	 3h	66 ^d

9		1a		70
10		1a		60
11		1a		45
12		1a		69
13	2c			85
14	2f	1b		87 ^c
15		1b		88

16	2a	 1c	 3p	73
			 3q	(1:1.1)
17	2g	 1d	 3s	70
18	2g	 1e	 3t	58
19	2c	 1f	 3u	66
20	2g	1f	 3v	69
21	 2n	1a	 3w	58
22	 2o	1a	 3x	54

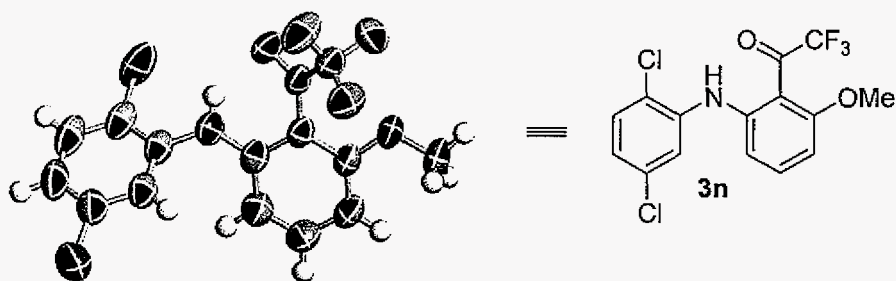
23		1b		66
24		1a		43
25		1a		74
				(1:1)
26		1a		0
27		1a		0
28		1a		0

^a Reaction conditions: 0.5 mmol of amide, 1.2 equiv of aryne precursor and 2.0 equiv of CsF in 5.0 mL of MeCN at room temperature for 4 h. ^b Isolated yield. ^c A 71% yield was obtained, when TBAF was used in THF. ^d X-ray crystallographic data for this compound are available.

yields of the corresponding insertion products (entries 17-20). This insertion reaction is

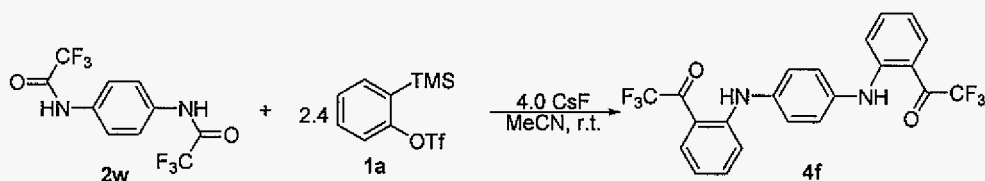
not limited to trifluoroacetamides, 2-chloro-2,2-difluoro-*p*-chloroacetanilide (**2n**), 2,2-difluoro-*p*-chloroacetanilide (**2o**), 2-chloro-2,2-difluoro-*p*-methylacetanilide (**2p**) and 2,2-difluoro-*p*-methylacetanilide (**2q**) have all reacted with the aryne precursor **1a** to afford good yields of the desired products (entries 21-24). Not only *N*-aryltrifluoroacetamides can react with a variety of arynes to generate the corresponding insertion product, *N*-benzyltrifluoroacetamide can also be employed in this process. It afforded the desired insertion product in a 37% yield, alongside a 37% yield of the direct *N*-arylation product (entry 25). However, acetanilides bearing fewer halogens or less electron-withdrawing halogens, such as *N*-phenyltrichloroacetamide, failed to undergo insertion (entry 26). *N*-Methyl-*N*-phenyltrifluoroacetamide is also totally inert in this insertion process. Apparently, the free proton in the amide is also very important for this insertion chemistry to occur (entry 27). As we mentioned before, the trifluoromethyl group in the amide substrates is very important for this C-N bond insertion chemistry to work, since trifluoromethyl is a strong electron-withdrawing group which can increase the acidity of the amides and also increase the electrophilicity of the carbonyl group in this amides (compare entries 3, 21 and 22).

Figure 2. X-Ray Structure for Compound (3n)



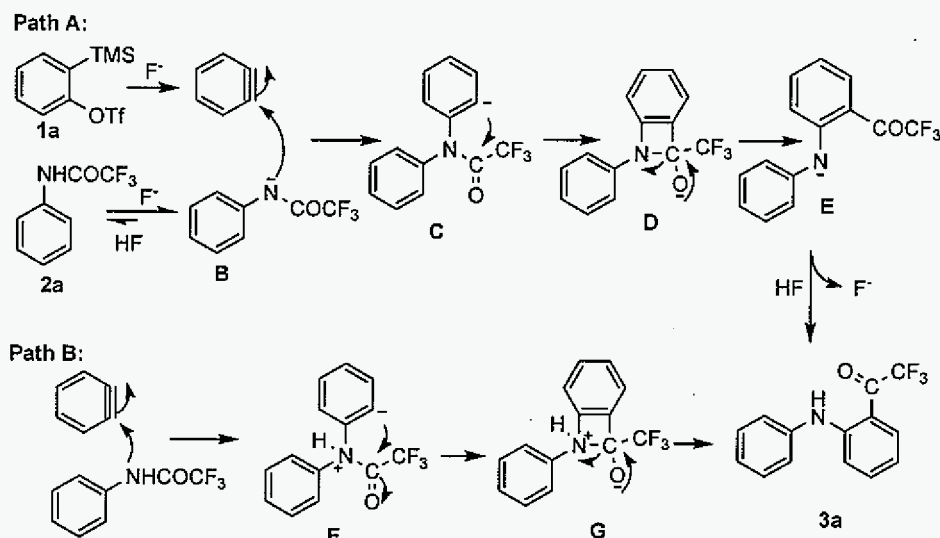
Interestingly, when *N,N'*-1,4-phenylenebis(2,2,2-trifluoroacetamide) (**3w**) was employed, we obtained only the double insertion product **4f** in moderate 48% yield (Scheme 10). When simple β -lactams, such as 2-azetidinone and 2-pyrrolidone, or 3,3-difluoro-4-phenyl-2-azetidinone, were employed, no insertion products were detected.

Scheme 10



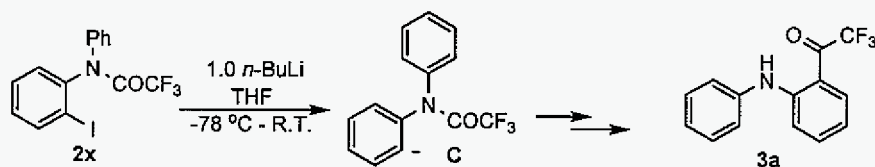
As indicated in Table 1, entries 26-28, no insertion products were detected when *N*-phenylacetamide, *N*-phenyltrichloroacetamide, or *N*-methyl-*N*-phenyltrifluoroacetamide were allowed to react with the benzyne precursor **1a**, even when adding an additional base, such as DBU. The presence of the CF₃ moiety is clearly critical to the success of this insertion chemistry, presumably because this strong electron-withdrawing group increases the acidity of the amide and also increases the electrophilicity of the carbonyl carbon of the amide. Based on our results, we propose the reaction mechanism shown in Scheme 11, Path A, although we cannot rule out Path B. Fluoride anion can react both with silylaryl triflate **1a** to generate benzyne and also act as a base to abstract the hydrogen on the amide nitrogen to afford anion **B**, which can attack the benzyne to produce intermediate **C**. Intermediate **C** can then undergo intramolecular nucleophilic attack on the carbonyl carbon to generate the unstable four-membered ring intermediate **D**, which readily undergoes ring opening and protonation to afford the final C-N insertion product **3a**.

Scheme 11



In order to obtain further evidence to support our mechanism, we allowed *N*-(2-iodophenyl)-*N*-phenyltrifluoroacetamide to react with 1.0 equiv of *n*-BuLi at a low temperature to generate the anionic intermediate **C** shown in mechanism Path A in Scheme 11. Subsequent rearrangement of intermediate **C** should afford ketone **3a**. Indeed, we obtained the desired product **3a** in a 45 % yield (Scheme 12).

Scheme 12

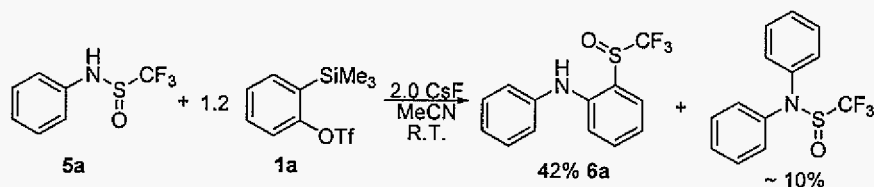


Intermolecular S-N Bond Addition of Sulfinamides to Arynes.

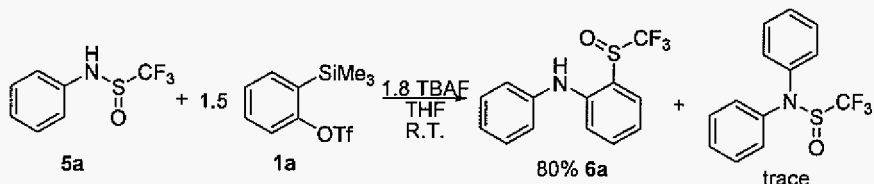
After examining the C-N addition of amides to arynes, we focused on trifluoromethanesulfinamides,¹³ which can be readily prepared from the corresponding aniline and trifluoromethanesulfinate salts.¹⁴ Because the highly electrophilic nature of the sulfur atom is enhanced by the CF₃ moiety, we expected that sulfinamides should undergo S-N addition to arynes. Indeed, when we allowed *N*-phenyl-trifluoromethanesulfinamide to

react with silylaryl triflate **1a** under our standard reaction conditions, the product of S-N addition to benzyne was obtained in a 42% yield, alongside about 10% of the direct *N*-arylated product (Scheme 13). Changing the ratio of the starting materials and the temperature of this reaction did not improve the yield of the desired insertion product. By using 1.5 equiv of the aryne precursor and 1.8 equiv of *n*-Bu₄NF (TBAF) as the fluoride source, instead of CsF, and THF as the solvent, we were able to obtain the desired insertion compound in an 80% yield in 30 min at room temperature (Scheme 14) (Table 2, entry 1).

Scheme 13



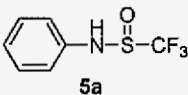
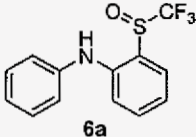
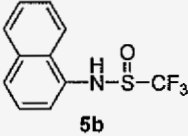
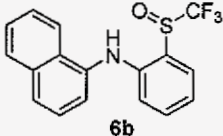
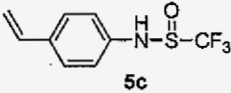
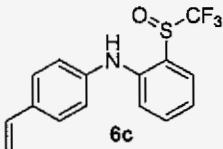
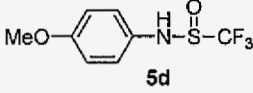
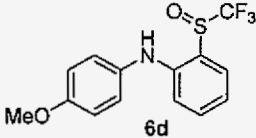
Scheme 14

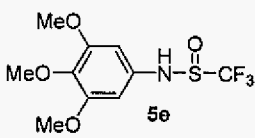
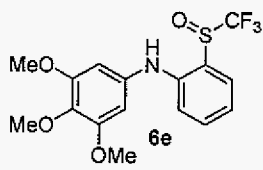
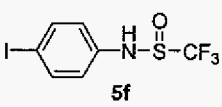
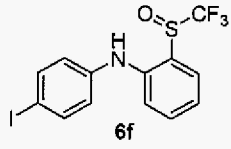
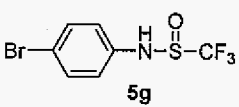
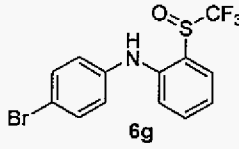
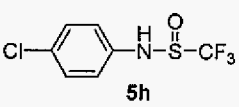
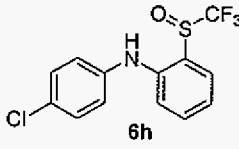

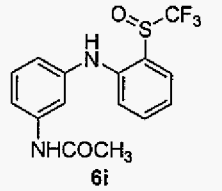
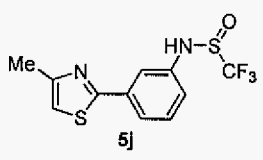
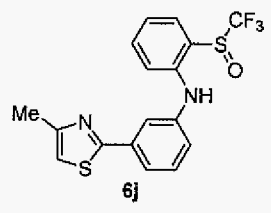
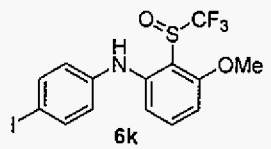
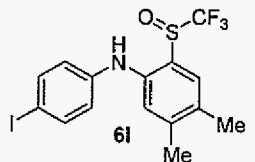


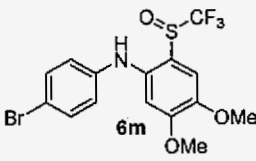
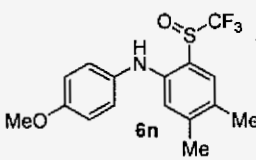
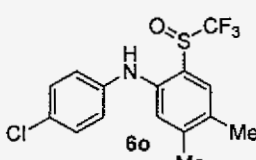
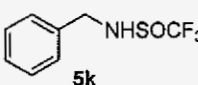
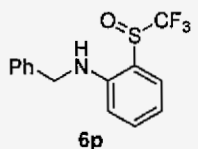
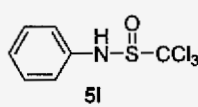
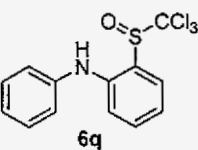
The scope and the limitations of this S-N sulfinamide bond addition to arynes has been examined and representative results are summarized in Table 2. All trifluoromethanesulfinamides work well with our standard aryne precursors to afford the corresponding S-N insertion products in high yields. Again substrates with electron-donating or electron-withdrawing groups both afford high yields of the desired products (entries 2-8). Substrates bearing halides are also no problem for this chemistry, and the corresponding insertion products can be obtained in very good yields (entries 6-8). Interestingly, benzyne

has been observed to react selectively with a sulfinamide bearing an acetamide group to afford only the S-N insertion product in a 70% yield, leaving the acetamide group untouched (entry 9). An interesting thiazole derivative also afforded a high yield of aryne insertion product (entry 10). Once again, these sulfinamides react with the substituted aryne precursors (**1b**, **1d** and **1e**) to produce the corresponding insertion products in good yields (entries 11-15). An *N*-alkylsulfinamide has also been shown to undergo this insertion chemistry, although the yield is a little lower (entry 16). However, a sulfinamide bearing less electron-withdrawing halogens, such as *N*-phenyltrichlorosulfinamide, failed to undergo insertion (entry 17).

Table 2. Addition of S-N Bond of Sulfinamides to Arynes.^a

entry	substrate	aryl triflate	product	% yield ^b
1	 5a	1a	 6a	80
2	 5b	1a	 6b	79
3	 5c	1a	 6c	66
4	 5d	1a	 6d	91

5	 5e	1a	 6e	79
6	 5f	1a	 6f	81
7	 5g	1a	 6g	83
8	 5h	1a	 6h	70
9	 5i	1a	 6i	70
10	 5j	1a	 6j	75
11	5f	1b	 6k	56
12	5f	1e	 6l	70

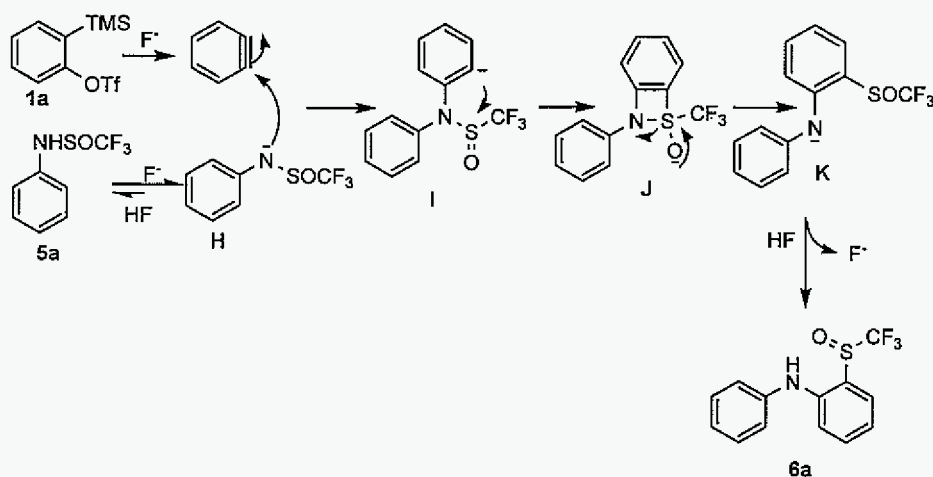
13	5g	1d		72
14	5d	1e		51
15	5h	1e		55
16		1a		41
17		1a		0

^a Reaction conditions: 0.5 mmol of sulfinamide, 1.5 equiv of aryne precursor and 1.8 equiv of TBAF in 5.0 mL of THF at room temperature for 30 min. ^b Isolated yield.

Based on the results shown in Table 2, we propose the reaction mechanism shown in Scheme 15 to account for this addition of the S-N bond of sulfinamides to arynes. Fluoride anion can react both with silylaryl triflate **1a** to generate benzyne and also act as a base to abstract the hydrogen on the sulfinamide nitrogen to afford anion **H**, which can attack the benzyne to produce intermediate **I**. Intermediate **I** can then undergo intramolecular nucleophilic attack on the sulfinyl sulfur to generate the unstable four-membered ring

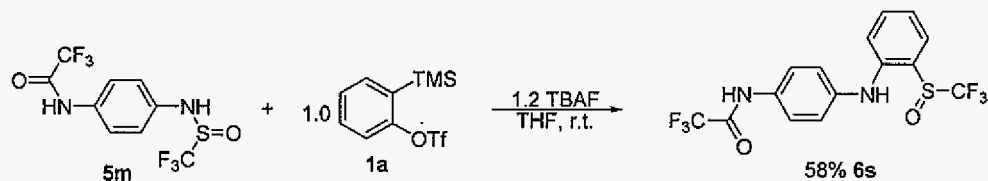
intermediate **J**, which readily undergoes ring opening and protonation to afford the final S-N insertion product **6a**.

Scheme 15



After having studied the scope and limitations of the addition of the C-N bond of amides and the S-N bond of sulfinamides to arynes, we studied the relative reactivity of these two groups. Substrate **5m** bearing both a trifluoroacetamide and a trifluoromethanesulfinamide group was allowed to react with 1.0 equiv of benzyne precursor **1a**, and 1.2 equiv of TBAF in THF. Only the S-N bond insertion product was obtained in a good yield, leaving the trifluoroacetamide group untouched (Scheme 16). When the base CsF was used, instead of TBAF, and MeCN was employed as the solvent, this reaction was very messy. Since addition of the C-N bond of amides to an aryne can also be obtained in pretty good yield, when TBAF is used in THF (Table 1, entry 15), it is reasonable to think that the trifluorosulfinamide group is more reactive than the trifluoroacetamide group under the same reaction conditions.

Scheme 16



Conclusions

In summary, we have developed an efficient, mild, transition metal-free method for the intermolecular C-N σ -bond addition of amides and S-N σ -bond addition of sulfinamides to arynes. Insertion products like those produced herein should be very useful in the preparation of Efavirenz derivatives¹⁵ and for the molecular recognition of anions.¹⁶ A variety of functional groups are compatible with the reaction conditions. We have also provided a reasonable stepwise mechanism for this interesting insertion chemistry

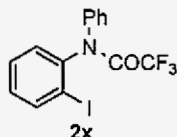
Experimental Section

General

The ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F) and visualization was effected with short wavelength UV light (254 nm) and basic KMnO_4 solution [3 g of KMnO_4 + 20 g of K_2CO_3 + 5 ml of NaOH (5 %) + 300 ml of H_2O]. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. All yields reported in the publication represent an average of at least two independent runs. CsF and acetonitrile were purchased from Sigma-Aldrich Co.. The product characterization data, and ^1H and ^{13}C NMR spectra for compounds 2w, 3a, 3c, 3i, 3j,

3l, 3n, 3o, 3p, 3q, 3s, 3t, 3y, 4f, 5a, 5d, 5f, 5g, 5h, 5j, 5k, 5m, 6a, 6d, 6f, 6j, 6m, 6o, 6p, and 6s have been reported in our previous communication.¹⁷

Preparation of the starting materials. All of the *N*-aryltrifluoroacetamides were either commercially available or easily prepared from commercially available materials.



***N*-(2-Iodophenyl)-*N*-phenyltrifluoroacetamide (2w).** To a solution of 1.48 g of of *N*-phenyl-2-iodoaniline (5.0 mmol) and 1.01 g of triethylamine (10 mmol) in 15 mL of CH₂Cl₂ at 0 °C was added 2.1 g of trifluoroacetic anhydride (10 mmol). The reaction mixture was stirred at room temperature of 1 d. The resulting solution was washed with brine (20 mL) and extracted with CH₂Cl₂ (20 mL). The combined CH₂Cl₂ fractions were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford 1.66 g of the desired product (85% yield) as a white solid: mp 93-94 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.00-7.62 (m, 8H), 7.94 (d, *J* = 7.8 Hz, 1H); ¹⁹F NMR: -68.0; IR (CDCl₃, cm⁻¹) 3064, 1711, 1593; Anal Calcd. for C₁₂H₉F₃INO: C, 42.99; H, 2.32; N, 3.58. Found: C, 42.97; H, 2.58; N, 3.65; HRMS *m/z* 391.9687 (calcd C₁₂H₉F₃INO, 391.9680).

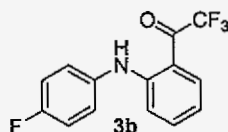
All of the *N*-aryltrifluoromethanesulfinamides have been prepared by the following procedure. To a solution of 1.56 g (10 mmol) of sodium trifluoromethanesulfinate (purity 97 %) in 10 mL of ethyl acetate was added at room temperature 0.467 mL of phosphoryl chloride. The resulting mixture was stirred for 5 min, then 5 mmol of aryl amine was added dropwise and the reaction mixture was stirred for an additional 30 min. The reaction mixture was then washed with brine (20 mL) and extracted with ethyl acetate (20 mL). The combined

ethyl acetate fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product.

General procedure for the intermolecular C-N addition of amides to arynes. To a solution of the *N*-aryltrifluoroacetamide (0.5 mmol) and silylaryl triflate (0.6 mmol) in acetonitrile (6 mL) was added CsF (1.0 mmol). The reaction was allowed to stir at room temperature for 4 h. The resulting solution was washed with brine (20 mL) and extracted with diethyl ether (20 mL). The combined ether fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product.

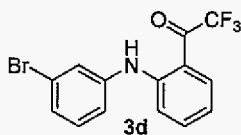
General procedure for the intermolecular S-N addition of sulfinamides to arynes. To a solution of the *N*-aryltrifluoromethanesulfinamide (0.5 mmol) and silylaryl triflate (0.75 mmol) in THF (6.0 mL) was slowly added tetra-*n*-butylammonium fluoride (TBAF, 0.9 mmol). The solution was allowed to stir at room temperature for 30 min and was then washed with brine (20 mL) and extracted with diethyl ether (20 mL). The combined ether fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product.

Characterization data:

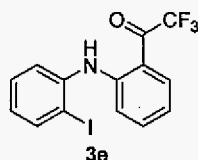


1-[2-(4-Fluorophenylamino)phenyl]trifluoroethanone (3b). The indicated compound was obtained in a 74% yield as a yellow solid: mp 75-77 °C; ^1H NMR (300 MHz, CDCl_3) δ 6.76 (td, $J = 8.1, 0.9$ Hz, 1H), 7.01-7.27 (m, 5H), 7.38 (td, $J = 8.4, 0.9$ Hz, 1H), 7.83-7.87 (m, 1H),

10.10 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 111.9, 114.3, 116.7 (d, $J = 22.5$ Hz), 117.1 (q, $J = 3.8$ Hz), 117.3 (q, $J = 289.5$ Hz), 127.1 (d, $J = 8.3$ Hz), 132.2 (q, $J = 4.0$ Hz), 134.9 (d, $J = 3.0$ Hz), 137.2, 157.2 (d, $J = 245.1$ Hz), 159.1, 181.2 (q, $J = 33.3$ Hz); ^{19}F NMR: -69.5, -16.4; IR (CDCl_3 , cm^{-1}) 3295, 3089, 1650, 1568; HRMS m/z 283.0624 (calcd $\text{C}_{14}\text{H}_9\text{F}_4\text{NO}$, 283.0620).



1-[2-(3-Bromophenylamino)phenyl]trifluoroethanone (3d). The indicated compound was obtained in a 70% yield as a yellow solid: mp 73-75 °C; ^1H NMR (300 MHz, CDCl_3) δ 6.82 (td, $J = 7.8, 0.9$ Hz, 1H), 7.17-7.34 (m, 4H), 7.41-7.46 (m, 2H), 7.85-7.89 (m, 1H), 10.15 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 112.7, 114.8, 117.2 (q, $J = 289.5$ Hz), 117.9, 122.7, 123.3, 127.0, 128.5, 131.1, 132.3 (q, $J = 4.0$ Hz), 137.3, 140.7, 150.5, 181.5 (q, $J = 33.3$ Hz); ^{19}F NMR: -69.5; IR (CDCl_3 , cm^{-1}) 3297, 3099, 1650, 1568; HRMS m/z 342.9824 (calcd $\text{C}_{14}\text{H}_9\text{BrF}_3\text{NO}$, 342.9819).

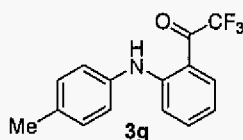


1-[2-(2-Iodophenylamino)phenyl]trifluoroethanone (3e). The indicated compound was obtained in a 76% yield as a yellow solid: mp 84-85 °C; ^1H NMR (300 MHz, CDCl_3) δ 6.82 (td, $J = 7.8, 0.9$ Hz, 1H), 6.93 (td, $J = 8.1, 2.1$ Hz, 1H), 7.00 (d, $J = 8.4$ Hz, 1H), 7.33-7.42 (m, 3H), 7.86-7.94 (m, 2H), 10.11 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 96.6, 112.7, 114.9, 117.3 (q, $J = 289.6$ Hz), 117.9, 125.4, 127.4, 129.4, 132.3 (q, $J = 4.0$ Hz), 137.1, 140.4, 141.1,

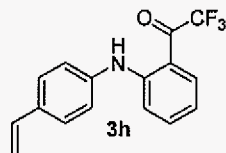
150.5, 181.4 (q, $J = 33.3$ Hz); ^{19}F NMR: -69.5; IR (CDCl_3 , cm^{-1}) 3286, 3077, 1655, 1515; HRMS m/z 390.9688 (calcd $\text{C}_{14}\text{H}_9\text{ClF}_3\text{NO}$, 390.9681).



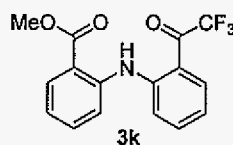
1-[2-(2,5-Dichlorophenylamino)phenyl]trifluoroethanone (3f). The indicated compound was obtained in a 78% yield as a yellow solid: mp 95-97 °C; ^1H NMR (300 MHz, CDCl_3) δ 6.92 (td, $J = 7.8, 0.9$ Hz, 1H), 7.06 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.27 (d, $J = 8.4$ Hz, 1H), 7.40 (d, $J = 8.4$ Hz, 1H), 7.48-7.53 (m, 2H), 7.90-7.94 (m, 1H), 10.18 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 113.9, 115.3, 117.1 (q, $J = 289.6$ Hz), 119.0, 123.1, 131.4, 132.5 (q, $J = 4.0$ Hz), 133.2, 137.3, 137.9, 148.7, 181.7 (q, $J = 33.3$ Hz); ^{19}F NMR: -69.5; IR (CDCl_3 , cm^{-1}) 3284, 3079, 1655, 1512; HRMS m/z 332.9939 (calcd $\text{C}_{14}\text{H}_8\text{Cl}_2\text{F}_3\text{NO}$, 332.9935).



1-[2-(4-Methylphenylamino)phenyl]trifluoroethanone (3g). The indicated compound was obtained in a 75% yield as a yellow solid: mp 76-78 °C; ^1H NMR (400 MHz, CDCl_3) δ 6.74 (td, $J = 7.8, 0.9$ Hz, 1H), 7.12-7.26 (m, 5H), 7.37 (t, $J = 8.4$ Hz, 1H), 7.84-7.87 (m, 1H), 10.21 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 114.6, 116.7, 117.4 (q, $J = 289.6$ Hz), 124.9, 130.4, 132.1 (q, $J = 4.0$ Hz), 135.8, 136.3, 137.1, 152.1, 181.0 (q, $J = 33.3$ Hz); ^{19}F NMR: -69.5; IR (CDCl_3 , cm^{-1}) 3306, 3030, 2924, 2858, 1658, 1518; HRMS m/z 279.0874 (calcd $\text{C}_{15}\text{H}_{11}\text{F}_3\text{NO}$, 279.0871).



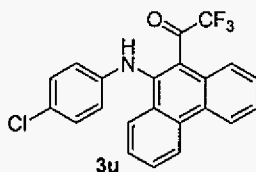
1-[2-(4-Vinylphenylamino)phenyl]trifluoroethanone (3h). The indicated compound was obtained in a 66% yield as a yellow solid: mp 74-76 °C; ^1H NMR (300 MHz, CDCl_3) δ 5.25 (d, $J = 10.8$ Hz, 1H), 5.73 (d, $J = 17.7$ Hz, 1H), 6.66-6.80 (m, 2H), 7.20-7.24 (m, 3H), 7.36-7.45 (m, 3H), 7.83-7.87 (m, 1H), 10.24 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 112.3, 113.9, 114.9, 117.3, 117.4 (q, $J = 289.6$ Hz), 124.3, 127.6, 132.2 (q, $J = 4.0$ Hz), 135.0, 136.2, 137.1, 138.6, 151.2, 181.2 (q, $J = 33.3$ Hz); ^{19}F NMR: -69.4; IR (CDCl_3 , cm^{-1}) 3300, 3032, 2924, 2856, 1658, 1518; HRMS m/z 291.0875 (calcd $\text{C}_{16}\text{H}_{11}\text{F}_3\text{NO}$, 291.0871).



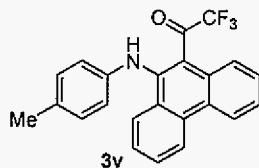
Methyl 2-[2-trifluoroacetylphenylamino]benzoate (3k). The indicated compound was obtained in a 45% yield as a yellow solid: mp 82-83 °C; ^1H NMR (300 MHz, CDCl_3) δ 3.96 (s, 3H), 6.92 (t, $J = 6.8$ Hz, 1H), 7.06 (t, $J = 6.4$ Hz, 1H), 7.45 (s, 2H), 7.58 (s, 2H), 7.91 (d, $J = 6.0$ Hz, 1H), 8.03 (d, $J = 8.0$ Hz, 1H), 11.52 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 52.3, 116.1, 117.1, 117.2 (q, $J = 289.5$ Hz), 119.2, 119.7, 120.4, 122.4, 122.9, 132.2 (q, $J = 4.1$ Hz), 133.3, 136.3, 142.2, 147.6, 167.4, 180.9 (q, $J = 33.6$ Hz); ^{19}F NMR: -69.9; IR (CDCl_3 , cm^{-1}) 3308, 2999, 2952, 2844, 1721, 1669, 1592; HRMS m/z 323.0774 (calcd $\text{C}_{16}\text{H}_{11}\text{F}_3\text{NO}_3$, 323.0769).



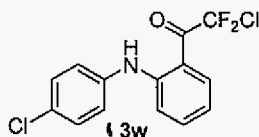
1-[2-(4-Chlorophenylamino)-6-methoxyphenyl]trifluoroethanone (3m). The indicated compound was obtained in an 85% yield as a yellow solid: mp 96-98 °C; ^1H NMR (300 MHz, CDCl_3) δ 3.87 (s, 3H), 6.34 (d, $J = 8.1$ Hz, 1H), 6.76 (d, $J = 8.4$ Hz, 1H), 7.13 (d, $J = 8.7$ Hz, 2H), 7.25-7.32 (m, 3H), 8.91 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.9, 101.0, 107.9, 108.5, 116.8 (q, $J = 287.9$ Hz), 124.2, 129.5, 129.7, 136.6, 138.7, 148.7, 161.9, 184.5 (q, $J = 36.4$ Hz); ^{19}F NMR: -74.1; IR (CDCl_3 , cm^{-1}) 3360, 3015, 2978, 2945, 2841, 1668, 1579; HRMS m/z 329.0435 (calcd $\text{C}_{15}\text{H}_{11}\text{F}_3\text{ClNO}_2$, 329.0430).



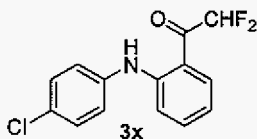
9-[10-(4-Chlorophenylamino)phenanthryl]trifluoroethanone (3u). The indicated compound was obtained in a 66% yield as a yellow solid: mp 105-106 °C; ^1H NMR (300 MHz, CDCl_3) δ 6.73-6.82 (m, 3H), 7.12-7.17 (m, 2H), 7.62-7.86 (m, 5H), 8.14 (dd, $J = 8.1$, 0.9 Hz, 1H), 8.96 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 114.9, 116.1 (q, $J = 289.9$ Hz), 119.8, 123.9, 124.0, 124.4, 125.0, 127.7, 127.9, 128.1, 128.9, 129.3, 129.4, 129.9, 133.1, 137.1, 147.2, 188.3 (q, $J = 36.8$ Hz); ^{19}F NMR: -76.5; IR (CDCl_3 , cm^{-1}) 3255, 2995, 2971, 2939, 2836, 1635, 1517; HRMS m/z 410.9408 (calcd $\text{C}_{22}\text{H}_{13}\text{ClF}_3\text{NO}$, 410.9402).



9-[10-(4-Methylphenylamino)phenanthryl]trifluoroethanone (3v). The indicated compound was obtained in a 69% yield as a yellow solid: mp 103-105 °C; ^1H NMR (300 MHz, CDCl_3) δ 2.21 (s, 3H), 5.97 (s, 1H), 6.55 (dt, $J = 8.4, 1.2$ Hz, 2H), 6.94 (d, $J = 8.1$ Hz, 2H), 7.47 (td, $J = 7.8, 0.9$ Hz, 1H), 7.59-7.71 (m, 4H), 7.94 (dd, $J = 8.1, 0.9$ Hz, 1H), 8.68 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.8, 115.8, 116.1 (q, $J = 290.4$ Hz), 123.5, 123.6, 125.0, 125.2, 127.6, 127.7, 128.1, 128.3, 128.4 (q, $J = 0.7$ Hz), 128.7, 129.1, 129.6, 130.1, 130.2, 133.1, 136.7, 143.7, 189.0 (q, $J = 30.3$ Hz); ^{19}F NMR: -76.5; IR (CDCl_3 , cm^{-1}) 3260, 2997, 2969, 2939, 2836, 1633, 1517; HRMS m/z 379.1190 (calcd $\text{C}_{23}\text{H}_{16}\text{F}_3\text{NO}$, 379.1184).

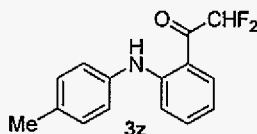


1-[2-(4-Chlorophenylamino)phenyl]-2'-chloro-2',2'-difluoroethanone (3w). The indicated compound was obtained in a 58% yield as a yellow solid: mp 72-73 °C; ^1H NMR (300 MHz, CDCl_3) δ 6.78 (td, $J = 8.1, 0.9$ Hz, 1H), 7.14-7.25 (m, 3H), 7.33-7.42 (m, 3H), 7.98-7.01 (m, 1H), 10.12 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 111.4, 114.8, 117.3, 120.6 (t, $J = 303.0$ Hz), 125.7, 129.9, 130.8, 132.6 (t, $J = 5.0$ Hz), 136.9, 137.9, 151.2, 182.5 (t, $J = 27.4$); IR (CDCl_3 , cm^{-1}) 3359, 3024, 2941, 2840, 1657; HRMS m/z 315.0033 (calcd $\text{C}_{14}\text{H}_9\text{Cl}_2\text{F}_2\text{NO}$, 315.0029).

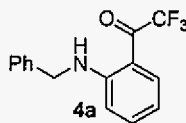


1-[2-(4-Chlorophenylamino)phenyl]-2,2'-difluoroethanone (3x). The indicated compound was obtained in a 54% yield as a yellow solid: mp 68-70 °C; ^1H NMR (300 MHz, CDCl_3) δ 6.39 (t, $J = 53.7$ Hz, 1H), 6.79 (t, $J = 7.8$ Hz, 1H), 7.15-7.42 (m, 6H), 7.90 (dd, $J =$

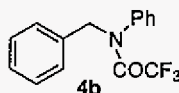
7.8, 1.2 Hz, 1H), 10.22 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 111.3 (t, $J = 252.0$ Hz), 114.2, 114.4, 125.4, 129.9, 130.4, 132.0 (t, $J = 4.3$ Hz), 136.7, 138.1, 150.1, 188.6 (t, $J = 23.6$ Hz); IR (CDCl_3 , cm^{-1}) 3368, 3026, 2940, 2842, 1656; HRMS m/z 281.0422 (calcd $\text{C}_{14}\text{H}_{10}\text{ClF}_2\text{NO}$, 281.0419).



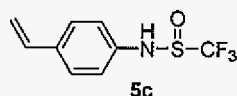
1-[2-(4-Methylphenylamino)phenyl]-2,2-difluoroethanone (3z). The indicated compound was obtained in a 43% yield as a yellow solid: mp 72-73 °C; ^1H NMR (300 MHz, CDCl_3) δ 2.36 (s, 3H), 6.40 (t, $J = 53.7$ Hz, 1H), 6.72 (td, $J = 7.8, 0.9$ Hz, 1H), 7.12-7.25 (m, 5H), 7.34 (td, $J = 7.8, 0.9$ Hz, 1H), 7.86 (dd, $J = 8.1, 1.2$ Hz, 1H), 10.24 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 21.2, 111.4 (t, $J = 252.0$ Hz), 113.6, 114.5, 116.6, 124.7, 130.4, 131.8 (t, $J = 4.2$ Hz), 135.3, 136.5, 136.6, 151.2, 188.2 (t, $J = 23.6$ Hz); IR (CDCl_3 , cm^{-1}) 3371, 3026, 2942, 2840, 1656; HRMS m/z 261.0970 (calcd $\text{C}_{15}\text{H}_{13}\text{F}_2\text{NO}$, 261.0965).



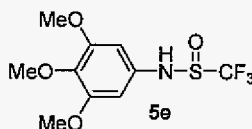
1-[2-(Benzylamino)phenyl]trifluoroethanone (4a). The indicated compound was obtained in a 37% yield as a yellow solid: mp 63-65 °C; ^1H NMR (300 MHz, CDCl_3) δ 4.51 (d, $J = 5.7$ Hz, 2H), 6.66 (td, $J = 8.1, 0.9$ Hz, 1H), 6.76 (d, $J = 8.7$ Hz, 1H), 7.24-7.43 (m, 6H), 7.78-7.82 (m, 1H), 9.13 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 47.2, 111.2, 112.9, 115.5, 117.7 (q, $J = 289.6$ Hz), 127.3, 127.8, 129.1, 132.4 (q, $J = 4.1$ Hz), 137.5, 137.7, 153.6, 180.9 (q, $J = 32.8$ Hz); IR (CDCl_3 , cm^{-1}) 3369, 3028, 2942, 2842, 1654; HRMS m/z 279.0874 (calcd $\text{C}_{15}\text{H}_{11}\text{F}_3\text{NO}$, 279.0871).



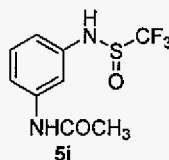
***N*-Benzyl-*N*-phenyltrifluoroacetamide (4b).** The indicated compound was obtained in a 37% yield as a yellow solid: mp 54-56 °C; ^1H NMR (300 MHz, CDCl_3) δ 4.90 (s, 2H), 6.98-7.00 (m, 2H), 7.15-7.18 (m, 2H), 7.27-7.36 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.7, 116.7 (q, $J = 286.9$ Hz), 128.4, 128.8 (q, $J = 1.0$ Hz), 128.8, 129.3, 129.4, 129.5, 135.5, 138.9, 157.2 (q, $J = 35.5$ Hz); IR (CDCl_3 , cm^{-1}) 3026, 2958, 2807, 1655; HRMS m/z 279.0874 (calcd $\text{C}_{15}\text{H}_{11}\text{F}_3\text{NO}$, 279.0871).



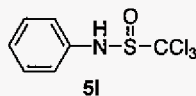
***N*-(4-Vinylphenyl)trifluoromethanesulfinamide (5c).** The indicated compound was obtained in an 84% yield as a white solid: mp 71-73 °C; ^1H NMR (300 MHz, CDCl_3) δ 5.24 (d, $J = 11.1$ Hz, 1H), 5.70 (d, $J = 17.7$ Hz, 1H), 6.62-6.72 (m, 1H), 6.94 (s, 1H), 7.04 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 114.2, 120.4, 123.8 (q, $J = 331.6$ Hz), 127.8, 135.1, 135.8, 137.8; ^{19}F NMR: -78.0; HRMS m/z 235.0282 (calcd $\text{C}_9\text{H}_8\text{F}_3\text{NOS}$, 235.0287).



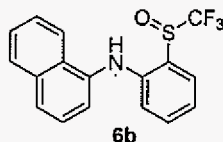
***N*-(3,4,5-Trimethoxyphenyl)trifluoromethanesulfinamide (5e).** The indicated compound was obtained in an 81% yield as a white solid: mp 94-95 °C; ^1H NMR (300 MHz, CDCl_3) δ 3.76 (s, 6H), 3.77 (s, 3H), 6.31 (s, 2H), 7.13 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 56.2, 61.1, 98.6, 119.4 (q, $J = 331.6$ Hz), 134.5, 135.8, 154.1; HRMS m/z 299.0444 (calcd $\text{C}_{10}\text{H}_{12}\text{F}_3\text{NO}_4\text{S}$, 299.0439).



***N*-[3-(Acetylamino)phenyl]trifluoromethanesulfinamide (5i).** The indicated compound was obtained in a 78% yield as a white solid: mp 113-115 °C; ^1H NMR (300 MHz, acetone- d_6) δ 3.41 (s, 3H), 6.94 (m, 1H), 7.26 (m, 2H), 7.80 (s, 1H), 9.09 (s, 1H), 9.38 (s, 1H); ^{13}C NMR (75 MHz, acetone- d_6) δ 23.7, 110.6, 114.3, 115.3, 124.3 (q, $J = 333.1$ Hz), 130.1, 140.2, 140.9, 169.1; ^{19}F NMR: -78.0; IR (CDCl_3 , cm^{-1}) 3320, 3212, 3149, 3097, 2852, 1673, 1609; HRMS m/z 266.0340 (calcd $\text{C}_9\text{H}_9\text{F}_3\text{N}_2\text{O}_2\text{S}$, 266.0336).

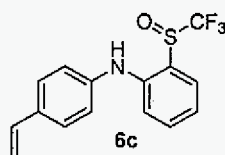


***N*-Phenyltrichloromethanesulfinamide (5l).** The indicated compound was obtained in a 78% yield as a white solid: mp 73-74 °C; ^1H NMR (300 MHz, CDCl_3) δ 6.48 (s, 1H), 7.10-7.15 (m, 3H), 7.30-7.36 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 109.9, 119.4, 124.7, 129.9, 139.0; IR (CDCl_3 , cm^{-1}) 3214, 3030, 2914, 1490, 1208; HRMS m/z 256.9240 (calcd $\text{C}_7\text{H}_6\text{Cl}_3\text{NOS}$, 256.9235).

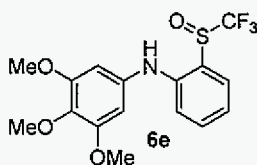


2-(1-Naphthylamino)phenyl trifluoromethyl sulfoxide (6b). The indicated compound was obtained in a 79% yield as a light yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 6.82 (td, $J = 8.0$, 0.8 Hz, 1H), 6.89 (d, $J = 8.4$ Hz, 1H), 7.30-7.53 (m, 6H), 7.70-7.72 (m, 1H), 7.86-7.89 (m, 1H), 7.98-8.00 (m, 1H), 8.68 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 114.0, 116.1, 118.2, 120.9, 122.6, 125.9, 126.0, 126.1 (q, $J = 336.2$ Hz), 126.7, 128.7, 129.6 (q, $J = 1.6$ Hz), 132.8,

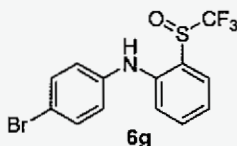
134.9, 135.1, 136.1, 150.2; ^{19}F NMR: -71.6; IR (CDCl_3 , cm^{-1}) 3316, 3058, 2921, 1594, 1578, 1460; HRMS m/z 335.0596 (calcd $\text{C}_{17}\text{H}_{12}\text{F}_3\text{NOS}$, 335.0591).



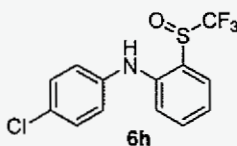
Trifluoromethyl 2-(4-vinylphenylamino)phenyl sulfoxide (6c). The indicated compound was obtained in a 66% yield as a light yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 5.19 (d, J = 11.4 Hz, 1H), 5.67 (d, J = 17.7 Hz, 1H), 6.63-6.73 (m, 1H), 6.89 (td, J = 7.5, 1.2 Hz, 1H), 7.11-7.14 (m, 2H), 7.30-7.43 (m, 5H), 8.21 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 112.9, 116.0 (q, J = 1.0 Hz), 116.8, 119.2, 121.5, 125.8 (q, J = 336.0 Hz), 127.6, 129.7 (q, J = 1.6 Hz), 133.4, 135.0, 136.3, 140.1, 148.1; ^{19}F NMR: -71.7; IR (CDCl_3 , cm^{-1}) 3332, 3008, 2962, 2909, 2836, 1595, 1512; HRMS m/z 311.0596 (calcd $\text{C}_{15}\text{H}_{12}\text{F}_3\text{NOS}$, 311.0591).



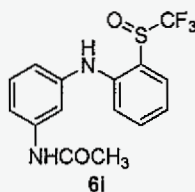
2-(3,4,5-Trimethoxyphenylamino)phenyl trifluoromethyl sulfoxide (6e). The indicated compound was obtained in a 79% yield as a light yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 3.83 (s, 6H), 3.84 (s, 3H), 6.42 (s, 2H), 6.87 (td, J = 8.4, 0.9 Hz, 1H), 7.24-7.28 (m, 1H), 7.36-7.44 (m, 2H), 8.16 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 56.4, 61.2, 100.3, 114.9 (q, J = 1.2 Hz), 116.2, 118.6, 125.9 (q, J = 336.0 Hz), 129.7 (q, J = 1.0 Hz), 135.1, 136.2, 148.9, 154.1; ^{19}F NMR: -71.7; IR (CDCl_3 , cm^{-1}) 3325, 3005, 2960, 2909, 2830, 1595, 1512; HRMS m/z 375.0757 (calcd $\text{C}_{16}\text{H}_{16}\text{F}_3\text{NO}_4\text{S}$, 375.0752).



2-(4-Bromophenylamino)phenyl trifluoromethyl sulfoxide (6g). The indicated compound was obtained in an 83% yield as a light yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 6.92 (td, $J = 7.2, 0.9$ Hz, 1H), 7.03-7.07 (m, 2H), 7.26 (d, $J = 8.1$ Hz, 1H), 7.38-7.44 (m, 4H), 8.19 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 116.2 (q, $J = 1.2$ Hz), 116.3, 116.7, 119.6, 123.1, 125.8 (q, $J = 336.0$ Hz), 129.8 (q, $J = 1.2$ Hz), 132.7, 135.1, 139.7, 147.8; ^{19}F NMR: -71.7; IR (CDCl_3 , cm^{-1}) 3335, 3022, 2960, 2909, 2836, 1590, 1512; HRMS m/z 362.9546 (calcd $\text{C}_{13}\text{H}_9\text{BrF}_3\text{NOS}$, 362.9540).

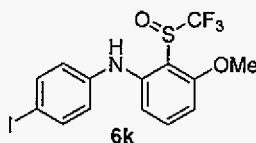


2-(4-Chlorophenylamino)phenyl trifluoromethyl sulfoxide (6h). The indicated compound was obtained in a 70% yield as a light yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 6.92 (t, $J = 7.2$ Hz, 1H), 7.09-7.12 (m, 2H), 7.22-7.31 (m, 3H), 7.37-7.44 (m, 2H), 8.21 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 115.9 (q, $J = 1.2$ Hz), 116.5, 119.4, 123.0, 125.8 (q, $J = 336.0$ Hz), 129.0, 129.8, 129.8 (q, $J = 1.0$ Hz), 135.1, 139.1, 148.1; ^{19}F NMR: -71.7; IR (CDCl_3 , cm^{-1}) 3335, 3022, 2960, 2909, 2836, 1590; HRMS m/z 319.0049 (calcd $\text{C}_{13}\text{H}_9\text{ClF}_3\text{NOS}$, 319.0045).

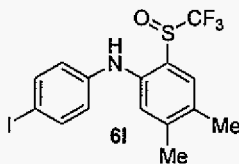


2-(3-Acetamidophenylamino)phenyl trifluoromethyl sulfoxide (6i). The indicated compound was obtained in a 70% yield (120 mg) as a light yellow solid: mp 91-93 $^{\circ}\text{C}$; ^1H

NMR (300 MHz, CDCl_3) δ 2.13 (s, 3H), 6.84-6.93 (m, 1H), 7.12-7.27 (m, 2H), 7.32-7.42 (m, 3H), 7.46 (s, 1H), 7.92 (s, 1H), 8.04 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.1, 147.6, 141.3, 139.4, 135.2, 130.1, 129.5, 125.7 (q, $J = 335.8$ Hz), 119.6, 117.3, 116.9, 116.5, 115.2, 112.7, 24.7; ^{19}F NMR: -71.8; IR (CDCl_3 , cm^{-1}) 3319, 3148, 3089, 2928, 1669, 1591, 1468; HRMS m/z 342.0455 (calcd $\text{C}_{15}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_2\text{S}$, 342.0649).

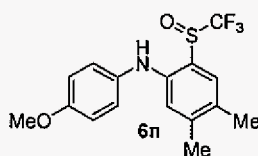


2-(4-Iodophenylamino)-6-methoxyphenyl trifluoromethyl sulfoxide (6k). The indicated compound was obtained in a 56% yield as a green oil; ^1H NMR (300 MHz, CDCl_3) δ 3.83 (s, 3H), 6.34 (d, $J = 8.4$ Hz, 1H), 6.81 (d, $J = 8.7$ Hz, 1H), 6.94 (d, $J = 8.4$ Hz, 2H), 7.25 (t, $J = 7.5$ Hz, 1H), 7.59 (d, $J = 8.7$ Hz, 2H), 8.98 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 56.5, 86.5, 101.2, 103.1 (q, $J = 1.5$ Hz), 108.7, 124.1, 126.3 (q, $J = 336.0$ Hz), 135.7, 138.5, 140.5, 150.1, 160.4; ^{19}F NMR: -71.7; IR (CDCl_3 , cm^{-1}) 3330, 3063, 3005, 2963, 2913, 2835, 1591, 1489; HRMS m/z 440.9511 (calcd $\text{C}_{14}\text{H}_{11}\text{IF}_3\text{NO}_2\text{S}$, 440.9507).



2-(4-Iodophenylamino)-4,5-dimethylphenyl trifluoromethyl sulfoxide (6l). The indicated compound was obtained in a 70% yield as slightly yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 2.22 (s, 3H), 2.23 (s, 3H), 6.88 (dt, $J = 8.7, 1.8$ Hz, 2H), 7.13 (s, 1H), 7.18 (s, 1H), 7.57 (dt, $J = 8.7, 1.8$ Hz, 2H), 7.77 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 19.1, 20.7, 85.1, 115.1 (q, $J = 1.7$ Hz), 119.2, 122.1, 125.2 (q, $J = 336.0$ Hz), 129.5, 129.8 (q, $J = 0.9$ Hz),

138.5, 141.4, 144.7, 145.2; ^{19}F NMR: -72.1; IR (CDCl_3 , cm^{-1}) 3324, 2972, 2860, 1593, 1492; HRMS m/z 438.9722 (calcd $\text{C}_{15}\text{H}_{13}\text{F}_3\text{INOS}$, 438.9714).



2-(4-Methoxyphenylamino)-4,5-dimethylphenyl trifluoromethyl sulfoxide (6n). The indicated compound was obtained in a 51% yield as a light yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 2.17 (s, 3H), 2.18 (s, 3H), 3.82 (s, 3H), 6.85 (s, 1H), 6.89 (d, $J = 8.8$ Hz, 2H), 7.09 (s, 1H), 7.10 (d, $J = 8.8$ Hz, 2H), 7.75 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.9, 20.7, 55.7, 111.6 (q, $J = 1.6$ Hz), 114.9, 116.7, 124.9, 125.9 (q, $J = 336.0$ Hz), 126.9, 129.6, 133.7, 145.1, 147.7, 156.7; ^{19}F NMR: -72.1; IR (CDCl_3 , cm^{-1}) 3325, 3065, 2972, 2911, 2835, 1590, 1489; HRMS m/z 343.0860 (calcd $\text{C}_{16}\text{H}_{16}\text{F}_3\text{NO}_2\text{S}$, 343.0854).

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CHAPTER 4. Synthesis of Indazoles by the [3+2] Cycloaddition of Diazo Compounds and Arynes

Based on a paper to be submitted to the *Journal of Organic Chemistry*¹⁴

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Abstract

The [3+2] cycloaddition of a variety of diazo compounds with silylaryl triflates in the presence of CsF or TBAF affords a wide variety of indazoles in good to excellent yields under mild reaction conditions.

Introduction

The indazole moiety is a frequently found subunit in pharmaceuticals with important biological,¹ and powerful pharmacological activities, such as anti-inflammatory,² anti-tumor,³ anti-HIV,⁴ anti-cancer,⁵ and anti-platelet activity.⁶ Recently, a variety of methods for the preparation of indazoles have been reported owing to the importance of indazoles in pharmaceutical development.⁷ However, the development of efficient and general methodologies for the synthesis of indazoles and derivatives has met with limited success and several limitations remain.⁷ For example, the need for harsh reaction conditions often limits the scope and applications. In addition, most of the present procedures involve several steps and the overall yields usually are not very good. Finally, special equipment is sometimes needed. Considering the limitations of previous procedures and the importance

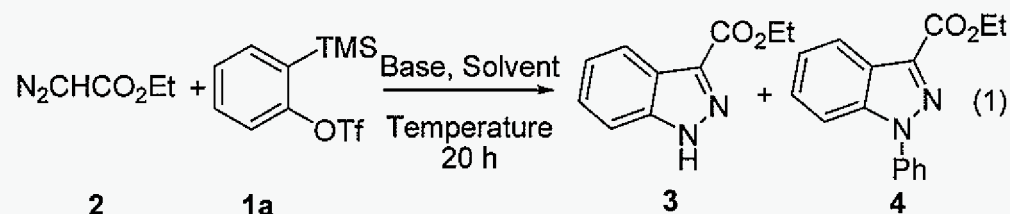
of such indazole derivatives, a simple, efficient and general method to synthesize indazoles and their derivatives would be quite attractive.

Recently, we have had considerable success using arynes prepared from *o*-(trimethylsilyl)aryl triflates under mild reaction conditions in a variety of synthetic processes.⁸ Continuing our interests in this chemistry, we decided to study aryne cycloaddition chemistry. The synthesis of indazoles by the [3+2] cycloaddition reaction of diazo compounds with *o*-(trimethylsilyl)aryl triflates should be a very attractive strategy, since the arynes can be generated under very mild reaction conditions. Although the reaction of benzyne and diazo compounds has been reported a long time ago,⁹ the process reported required the use of an explosive *o*-benzenediazonium carboxylate as the benzyne precursors and only one example using an *o*-benzenediazonium carboxylate and ethyl diazoacetate was reported and no yield was indicated. Herein, we wish to report our recent results on the synthesis of indazoles and their derivatives by the [3+2] cycloaddition reaction of diazo compounds and arynes under very mild reaction conditions, which affords excellent yields of indazoles.

Results and Discussion

We first allowed ethyl diazoacetate (**2**) to react with CsF and 1.2 equiv of 2-(trimethylsilyl)phenyl triflate (**1a**) in acetonitrile at room temperature for 20 h. A 1:1.2 mixture of ethyl indazole-3-carboxylate (**3**) and ethyl *N*-phenylindazole-3-carboxylate (**4**) were obtained in a 66% yield (Table 1, entry 1) (eq 1).

Table 1. Optimization of the Synthesis of Indazoles **3** and **4** (eq 1).^a



entry	2 (equiv)	1a (equiv)	base (equiv)	solvent	temp (°C)	3^b (%)	4^b (%)
1	1.0	1.2	CsF (2)	MeCN	rt	30	36
2	1.0	2.4	CsF (4)	MeCN	rt	0	97
3	1.2	1.0	CsF (2)	MeCN	rt	38	28
4	1.2	1.0	CsF (2)	MeCN	80	10	43
5	1.5	1.0	CsF (2)	MeCN	rt	55	17
6	1.2	1.0	TBAF (1.2)	THF	rt	36	30
7	1.2	1.0	TBAF (1.2)	THF	-78 °C-rt	78	8
8	1.5	1.0	TBAF (1.2)	THF	-78 °C-rt	85	<5

^a Reaction conditions: 0.3 mmol of silylphenyl triflate **1a**, the indicated amount of compound **2**, the base and 4.0 mL of solvent were stirred at shown temperature for 20 h. ^b Isolated yield.

The *N*-arylated indazole compound **4** can be obtained in an excellent yield from compound **2** by reacting **2** with twice as much of the benzyne precursor. If 2.4 equiv of silylaryl triflate **1a** was allowed to react with ethyl diazoacetate, only *N*-arylated indazole **4** was formed in a 97% yield (Table 1, entry 2). Since 1*H*-indazole derivatives, such as compound **3**, can be very easily functionalized, they are very important intermediates for the synthesis of a variety of bioactive compounds. Thus, our immediate efforts focused on improving the yield of ethyl indazole-3-carboxylate (**3**) (eq 1). In order to limit generation of the *N*-arylated compound, we used an excess of ethyl diazoacetate in subsequent reactions. When 1.2 equiv of ethyl diazoacetate were employed, *N*-phenylindazole **4** was still obtained in a 28% yield, and the desired cycloaddition product was produced in a 38% yield (Table 1, entry 3). When the same reaction was performed at 80 °C, the reaction favors formation of the *N*-arylated product **4**. Only 10% of the cycloaddition product **3** was obtained (Table 1, entry 4). Obviously, running this reaction at a lower temperature affords a higher yield of

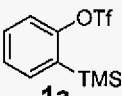
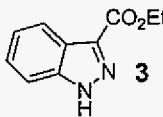
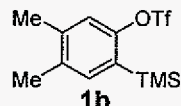
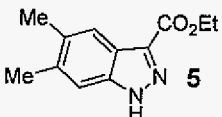
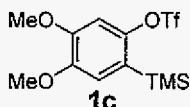
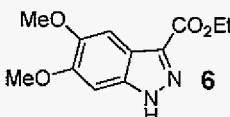
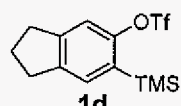
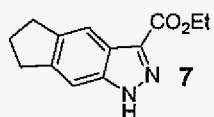
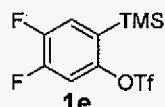
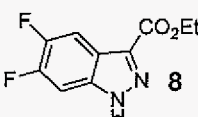
cycloaddition product **3** and decreases the amount of compound **4** (compare entries 3 and 4). The solvent THF and the fluoride source TBAF were next examined, since reactions run under these conditions can be performed at a lower temperature. When the reaction using THF and TBAF was performed at -78 °C and then allowed to warm to room temperature, the desired compound **3** could be obtained in a 78% yield and only a small amount of the *N*-arylated product was detected (entry 7). If 1.5 equiv of ethyl diazoacetate was employed under the same reaction conditions, an 85% yield of the desired compound **3** is obtained (entry 8). On the basis of the above optimization efforts, the combination of 2-(trimethylsilyl)phenyl triflate (0.3 mmol) (**1a**), 1.5 equiv of ethyl diazoacetate and 1.2 equiv of TBAF in 4 mL of THF when allowed to react from -78 °C to room temperature gave the best yield of the cycloaddition product **3**.

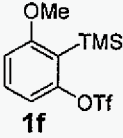
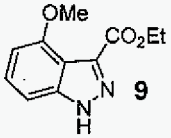
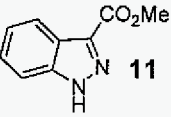
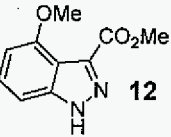
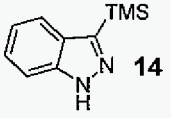
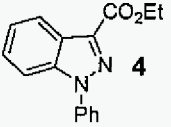
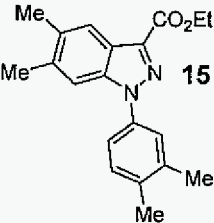
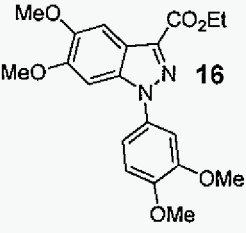
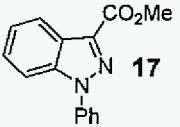
Having gained an understanding of the factors that influence this process, we have explored the scope and limitations of this methodology. The results are summarized in Table 2. We first allowed a variety of silylaryl triflates (**1a-f**) to react with ethyl diazoacetate under reaction conditions favoring the 1*H*-indazole product (entries 1-6). The reaction between electron-rich aryne precursors and ethyl diazoacetate gives very high yields of the cycloaddition products (entries 1-4). When electron-poor aryne precursor **1e** was employed, only a 45% yield of the corresponding cycloaddition product was obtained and several other unidentified products were also generated (entry 5). If the 3-methoxy aryne precursor **1f** was subjected to the reaction with ethyl diazoacetate, only one isomer of the cycloaddition product was isolated in a 58% yield. The regiochemistry observed arises from the nucleophile attack at the position *meta* to the methoxy group of the aryne as noted in a number of previous reactions with this aryne precursor (entry 6). Other diazo compounds

have also been examined in our cycloaddition chemistry. For example, methyl diazoacetate also reacts well with benzyne to generate the corresponding cycloadduct in a 76% yield (entry 7). However, when (trimethylsilyl)diazomethane was allowed to react with benzyne under the same reaction conditions, no cycloaddition product was detected (entry 9).

As shown in Table 1, entry 2, when an excess of the aryne precursor is employed in this cycloaddition chemistry, *N*-arylated indazoles can be obtained in one pot in very high yields by using CsF as the base in MeCN at room temperature (Table 2, entries 10-13). As indicated a variety of aryne precursors can be utilized and excellent yields are obtained in all cases.

Table 2. Synthesis of Indazoles^a

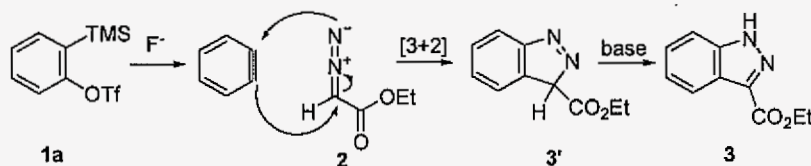
entry	diazo compound	aryne precursor	fluoride (equiv)	solvent	product	% isolated yield
1	$\text{N}_2\text{CHCO}_2\text{Et}$ 1	 1a	TBAF (1.2)	THF	 3	85
2	1	 1b	TBAF (1.2)	THF	 5	87
3	1	 1c	TBAF (1.2)	THF	 6	84
4	1	 1d	TBAF (1.2)	THF	 7	80
5	1	 1e	TBAF (1.2)	THF	 8	45

6	1		TBAF (1.2)	THF		58
7	$\text{N}_2\text{CHCO}_2\text{Me}$ 10	1a	TBAF (1.2)	THF		76
8	10	1f	TBAF (1.2)	THF		65
9	N_2CHTMS 13	1a	TBAF (1.2)	THF		0
10	1	1a	CsF (4.0)	MeCN		97 ^b
11	1	1b	CsF (4.0)	MeCN		88 ^b
12	1	1c	CsF (4.0)	MeCN		94 ^b
13	10	1a	CsF (4.0)	MeCN		92 ^b

^a Reaction conditions: 0.3 mmol of aryl triflate is allowed to react with 1.5 equiv of the diazo compound and 1.2 equiv of TBAF in 4.0 mL of THF and the reaction temperature is allowed to warm up from -78 °C to room temperature. ^b 0.3 Mmol of the diazo compound is allowed to react with 2.4 equiv of the aryl triflate and 4.0 equiv of CsF in MeCN at room temperature for 1 d.

As to the mechanism of this cycloaddition chemistry, ethyl diazoacetate and benzyne first undergo [3+2] cycloaddition to generate compound **3'**, which can undergo a 1,3-hydrogen shift under the basic conditions to yield the corresponding indazole **3** (Scheme 1). If an excess of the benzyne is employed, indazole **3** reacts further with the excess benzyne to afford the *N*-arylated indazole.

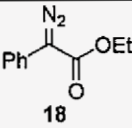
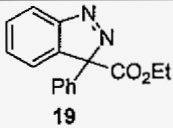
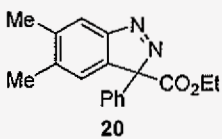
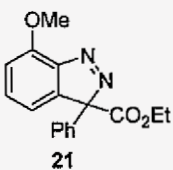
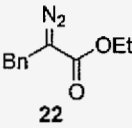
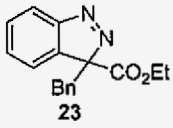

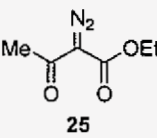
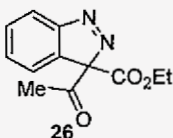
Scheme 1

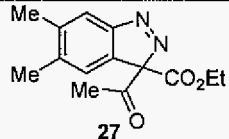

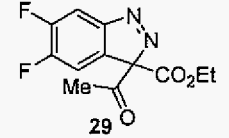
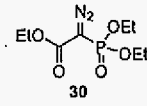
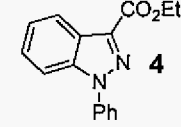
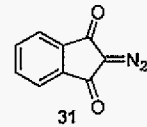
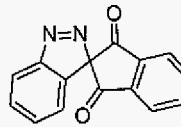


We have also examined the [3+2] cycloaddition of substrates, which do not have the activated α -hydrogen. The results are summarized in Table 3. Ethyl α -diazophenylacetate reacts quite efficiently to afford the cycloaddition product in a 76% yield (entry 1). When cycloaddition between the dimethyl-substituted aryne precursor and ethyl α -diazophenylacetate was performed, the desired product (**20**) was isolated in a 55% yield (entry 2). Only a moderate yield of the cycloaddition product was obtained when the 3-methoxy aryne precursor was employed (entry 3). Similarly, ethyl α -diazobenzylacetate also affords higher yields with the benzyne precursor **1a** (84% yield) than the 3-methoxy substituted aryne precursor **1f** (56% yield) (entries 4 and 5). Ethyl diazoacetoacetate also

affords excellent yields with most of the aryne precursors, except for the difluoro-substituted aryne precursor **1e**, which failed to give any of the desired product (entries 6-9). Interestingly, when triethyl diazophosphonoacetate was allowed to react with aryne precursor **1a**, we did not obtain the corresponding cycloaddition product. Instead the *N*-arylated indazole **4** was obtained in a 45% yield (entry 10). The reason why the phosphonate group is lost is not clear at present. Only the starting material was recovered, when 2-diazo-1,3-indanedione was employed in our cycloaddition process (entry 11).

Table 3. Synthesis of 3,3-Disubstituted Indazoles^a

entry	substrate	aryl triflate	product	% isolated yield
1	 18	1a	 19	76
2	18	1b	 20	55
3	18	1f	 21	44
4	 22	1a	 23	84
5	22	1f	 24	56
6	 25	1a	 26	85

7	25	1b	 27	85
8	25	1c	 28	92
9	25	1e	 29	0
10	 30	1a	 4	45 ^b
11	 31	1a	 32	0 ^c

^a Reaction conditions: 0.3 mmol of the diazo compound is allowed to react with 1.2 equiv of the aryl triflate and 2.0 equiv of CsF in MeCN at room temperature for 1 day. ^b A 55% yield of the product shown in the table was obtained, when 2.4 equiv of the aryl triflate was employed. ^c An 85% yield of starting material was recovered.

Conclusions

In summary, an efficient route to synthesize a variety of indazoles and their derivatives has been developed. It involves the reaction of a variety of diazo compounds with silylaryl triflates in the presence of CsF or TBAF to afford the corresponding [3+2] cycloadducts in good to excellent yields. This methodology provides a useful new route to indazoles, which should find application in the construction of molecules with interesting biological properties and pharmaceutical potential.

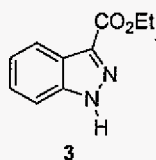
Experimental Section

General

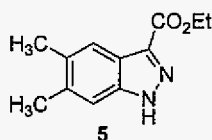
The ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F) and visualization was effected with short wavelength UV light (254 nm) and basic KMnO_4 solution [3 g of KMnO_4 + 20 g of K_2CO_3 + 5 ml of NaOH (5 %) + 300 ml of H_2O]. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. All yields reported in this publication represent an average of at least two independent runs. CsF and acetonitrile were purchased from Sigma-Aldrich Co..

Preparation of the starting materials. All of the diazoacetate substrates were either commercially available or easily prepared from commercially available materials (**18**,¹¹ **22**,¹¹ **30**¹² and **31**¹²).

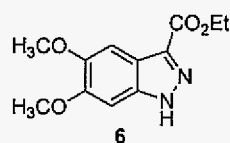
General procedure for the synthesis of the indazoles. To a solution of THF (4 mL), the silylaryl triflate (0.3 mmol) and the ethyl diazoacetate (0.45 mmol) at $-78\text{ }^\circ\text{C}$ was slowly added TBAF (0.36 mmol). The reaction mixture was stirred and allowed to gradually warm up to room temperature and stirred for 10 h. The resulting solution was washed with brine (20 mL) and extracted with diethyl ether (20 mL). The combined ether fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product.

Characterization data:

Ethyl 1*H*-indazole-3-carboxylate (3). The indicated compound was obtained in an 85% yield as a white solid: mp 132-134 °C (lit.¹⁰ 130 °C); the ¹H and ¹³C NMR spectra match the literature data.¹⁰

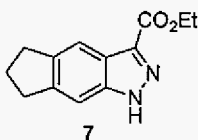


Ethyl 5,6-dimethyl-1*H*-indazole-3-carboxylate (5). The indicated compound was obtained in an 87% yield as a white solid: mp 197-199 °C (lit.¹³ 201 °C); ¹H NMR (300 MHz, acetone-*d*₆) δ 1.34 (t, *J* = 7.2 Hz, 3H), 2.31 (s, 3H), 2.32 (s, 3H), 4.34 (q, *J* = 7.2 Hz, 2H), 7.39 (s, 1H), 7.78 (s, 1H), 13.62 (s, 1H); ¹³C NMR (75 MHz, acetone-*d*₆) δ 14.9, 20.6, 20.9, 60.7, 111.1, 120.8, 121.6, 132.6, 135.1, 136.9, 140.9, 163.1; IR (CDCl₃, cm⁻¹) 3006, 2955, 2843, 1711, 1635; HRMS *m/z* 218.0819 (calcd C₁₂H₁₄N₂O₂, 218.1055).

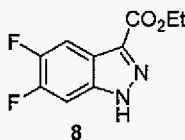


Ethyl 5,6-dimethoxy-1*H*-indazole-3-carboxylate (6). The indicated compound was obtained in an 84% yield as a white solid: mp 205-208 °C; ¹H NMR (300 MHz, acetone-*d*₆) δ 1.34 (t, *J* = 7.2 Hz, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 4.34 (q, *J* = 7.2 Hz, 2H), 7.02 (s, 1H), 7.35 (s, 1H), 13.55 (s, 1H); ¹³C NMR (75 MHz, acetone-*d*₆) δ 14.9, 56.1, 56.3, 60.7, 92.6, 100.6,

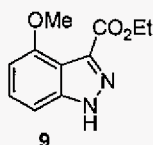
116.6, 135.2, 137.1, 148.1, 151.2, 163.3; IR (CDCl₃, cm⁻¹) 3012, 2959, 2931, 2850, 1711, 1509; HRMS *m/z* 250.0957 (calcd C₁₂H₁₄N₂O₄, 250.0953).



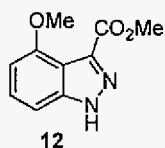
Ethyl 1,5,6,7-tetrahydrocyclopenta[f]indazole-3-carboxylate (7). The indicated compound was obtained in an 80% yield as a white solid: mp 172-173 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.47 (t, *J* = 7.6 Hz, 3H), 3.80 (p, *J* = 7.2 Hz, 2H), 2.98-3.03 (m, 4H), 4.53 (q, *J* = 7.2 Hz, 2H), 7.50 (s, 1H), 7.96 (s, 1H), 12.33 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 14.7, 26.8, 32.5, 33.1, 61.2, 106.1, 116.0, 122.3, 141.1, 141.7, 145.6, 163.6; IR (CDCl₃, cm⁻¹) 3006, 2955, 2843, 1711, 1636; HRMS *m/z* 230.1058 (calcd C₁₃H₁₄N₂O₂, 230.1055).



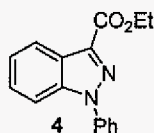
Ethyl 5,6-difluoro-1H-indazole-3-carboxylate (8). The indicated compound was obtained in a 45% yield as a white solid: mp 195-197 °C; ¹H NMR (400 MHz, acetone-d₆) δ 1.43 (t, *J* = 7.2 Hz, 3H), 4.45 (q, *J* = 7.2 Hz, 2H), 7.66-7.70 (m, 1H), 7.94-7.98 (m, 1H), 13.11 (s, 1H); ¹³C NMR (100 MHz, acetone-d₆) δ 14.0, 60.7, 98.9 (d, *J* = 21.6 Hz), 107.7 (d, *J* = 19.8 Hz), 118.3, 137.1 (d, *J* = 9.9 Hz), 147.1 (d, *J* = 15.7 Hz), 149.6, 152.2 (d, *J* = 16.9 Hz), 162.1; IR (CDCl₃, cm⁻¹) 3008, 2962, 2855, 1713, 1509; HRMS *m/z* 226.0558 (calcd C₁₀H₈F₂N₂O₂, 226.0553).



Ethyl 4-methoxy-1*H*-indazole-3-carboxylate (9). The indicated compound was obtained in a 58% yield as a white solid: mp 114-116 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.39 (t, *J* = 7.2 Hz, 3H), 3.89 (s, 3H), 4.47 (q, *J* = 7.2 Hz, 2H), 6.69 (d, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H); 11.77 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 14.5, 55.7, 61.2, 105.6, 113.9, 124.2, 124.5, 133.4, 136.9, 145.6, 163.1; IR (CDCl₃, cm⁻¹) 3007, 2931, 2852, 2637, 1710, 1588; HRMS *m/z* 220.0852 (calcd C₁₁H₁₂N₂O₃, 220.0848).

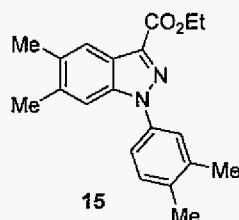


Methyl 4-methoxy-1*H*-indazole-3-carboxylate (12). The indicated compound was obtained in a 65% yield as a white solid: mp 110-113 °C; ¹H NMR (300 MHz, CDCl₃) δ 3.98 (s, 3H), 4.03 (s, 3H), 6.78 (d, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 11.10 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 52.1, 55.5, 105.5, 113.6, 124.1, 124.2, 133.2, 136.7, 145.2, 163.1; IR (CDCl₃, cm⁻¹) 3007, 2931, 2852, 1710, 1588; HRMS *m/z* 220.0695 (calcd C₁₀H₁₀N₂O₃, 206.0691).

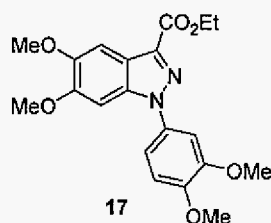


Ethyl 1-phenyl-1*H*-indazole-3-carboxylate (4). The indicated compound was obtained in a 97% yield as a white solid: mp 112-113 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.48 (t, *J* = 7.2 Hz, 3H), 4.54 (q, *J* = 7.2 Hz, 2H), 7.32-7.54 (m, 5H), 7.66-7.73 (m, 3H), 8.29 (dd, *J* = 8.0, 0.8 Hz,

1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.7, 61.4, 111.1, 122.7, 123.8, 124.1, 124.6, 127.8, 128.2, 129.7, 137.2, 139.4, 140.4, 162.8; IR (CDCl_3 , cm^{-1}) 3058, 3045, 2978, 2934, 2897, 1725, 1593, 1478; HRMS m/z 266.1060 (calcd $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2$, 266.1055).

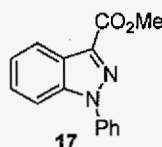


Ethyl 5,6-dimethyl-1-(3,4-dimethylphenyl)indazole-3-carboxylate (15). The indicated compound was obtained in an 88% yield as a white solid: mp 130-132 °C; ^1H NMR (300 MHz, CDCl_3) δ 1.48 (t, $J = 7.2$ Hz, 3H), 2.31 (s, 3H), 2.33 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 4.53 (q, $J = 7.2$ Hz, 2H), 7.24-7.27 (m, 1H), 7.39-7.42 (s, 2H), 7.49 (s, 1H), 8.01 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.7, 19.7, 20.1, 20.4, 21.2, 61.2, 110.9, 121.2, 121.7, 123.4, 125.3, 130.5, 133.3, 136.1, 136.6, 137.4, 137.7, 138.2, 139.8, 163.2; IR (CDCl_3 , cm^{-1}) 2979, 2922, 2860, 2732, 1711, 1613; HRMS m/z 322.1685 (calcd $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$, 322.1681).

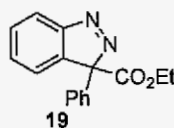


Ethyl 5,6-dimethoxy-1-(3,4-dimethoxyphenyl)indazole-3-carboxylate (17). The indicated compound was obtained in a 94% yield as a white solid: mp 155-157 °C; ^1H NMR (300 MHz, CDCl_3) δ 1.40 (t, $J = 7.2$ Hz, 3H), 3.83 (s, 3H), 3.86 (s, 6H), 3.90 (s, 3H), 4.43 (q, $J = 7.2$ Hz, 2H), 6.86-6.91 (m, 2H), 7.08-7.14 (m, 2H), 7.50 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.6, 56.2, 56.3, 56.4, 61.1, 91.9, 101.1, 108.6, 111.2, 116.1, 118.2, 132.6, 135.8, 136.3, 148.3,

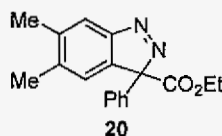
149.0, 149.8, 151.5, 163.2; IR (CDCl₃, cm⁻¹) 3089, 3009, 2938, 2907, 2835, 2040, 1708, 1601; HRMS m/z 386.1482 (calcd C₂₀H₂₂N₂O₆, 386.1477).



Methyl 1-phenyl-1H-indazole-3-carboxylate (17). The indicated compound was obtained in a 92% yield as a white solid: mp 108-110 °C; ¹H NMR (400 MHz, CDCl₃) δ 4.07 (s, 3H), 7.36-7.50 (m, 3H), 7.54-7.58 (m, 2H), 7.10-7.75 (m, 3H), 8.32 (dd, *J* = 8.4, 0.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 52.4, 111.1, 122.6, 124.0, 124.1, 124.6, 127.9, 128.3, 129.7, 136.9, 139.4, 140.4, 163.3; IR (CDCl₃, cm⁻¹) 3056, 3044, 2978, 2934, 2897, 1725, 1593, 1475; HRMS m/z 252.0903 (calcd C₁₅H₁₂N₂O₂, 252.0898).



Ethyl 3-phenyl-3H-indazole-3-carboxylate (19). The indicated compound was obtained in a 76% yield as a white solid: mp 58-59 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.23 (t, *J* = 7.2 Hz, 3H), 4.20-4.27 (m, 2H), 7.35-7.38 (m, 3H), 7.48-7.51 (m, 2H), 7.59-7.63 (m, 2H), 7.86-7.89 (m, 1H), 8.15-8.18 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 13.8, 62.7, 101.1, 122.1, 124.8, 127.3, 128.8, 128.9, 130.0, 120.3, 132.9, 137.7, 157.5, 166.7; IR (CDCl₃, cm⁻¹) 3016, 2926, 2856, 1734, 1641; HRMS m/z 266.1060 (calcd C₁₆H₁₄N₂O₂, 266.1055).

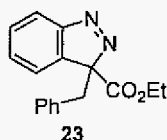


Ethyl 5,6-dimethyl-3-phenyl-3H-indazole-3-carboxylate (20). The indicated compound was obtained in a 55% yield as a white solid: mp 145-148 °C; ¹H NMR (300 MHz, CDCl₃) δ

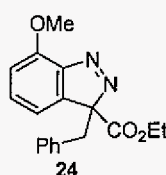
1.53 (t, $J = 7.2$ Hz, 3H), 2.40 (s, 3H), 2.45 (s, 3H), 4.61 (q, $J = 7.2$ Hz, 2H), 7.43-7.55 (m, 3H), 7.70 (s, 1H), 7.95-7.98 (m, 2H), 8.09 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.5, 20.2, 20.9, 63.8, 114.9, 121.1, 122.8, 128.3, 128.7, 129.3, 132.0, 133.5, 139.2, 140.4, 150.2, 151.1; IR (CDCl_3 , cm^{-1}) 3016, 2928, 2857, 1734, 1638; HRMS m/z 294.1372 (calcd $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2$, 294.1368).



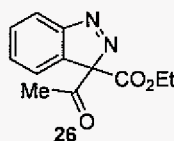
Ethyl 7-methoxy-3-phenyl-3H-indazole-3-carboxylate (21). The indicated compound was obtained in a 44% yield as a yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 1.23 (t, $J = 7.2$ Hz, 3H), 4.20 (s, 3H), 4.14-4.32 (m, 2H), 7.09 (d, $J = 8.1$ Hz, 1H), 7.32-7.54 (m, 7H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.9, 57.4, 62.7, 100.9, 114.1, 116.8, 127.3, 128.8, 128.9, 132.2, 133.1, 140.6, 146.2, 153.0, 166.9; IR (CDCl_3 , cm^{-1}) 2981, 2939, 2845, 1736, 1614; HRMS m/z 296.1167 (calcd $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3$, 296.1161).



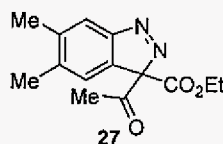
Ethyl 3-benzyl-3H-indazole-3-carboxylate (23). The indicated compound was obtained in a 76% yield as a yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 1.17 (t, $J = 7.2$ Hz, 3H), 3.62 (d, $J = 13.8$ Hz, 1H), 3.77 (d, $J = 13.7$ Hz, 1H), 4.07-4.25 (m, 2H), 6.92-7.01 (m, 2H), 7.08-7.14 (m, 3H), 7.43-7.58 (m, 3H), 7.94-8.01 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.9, 40.9, 62.4, 98.6, 121.6, 123.2, 127.1, 127.8, 129.5, 129.9, 130.1, 133.3, 138.4, 157.5, 166.8; IR (CDCl_3 , cm^{-1}) 3016, 2926, 2851, 1734, 1641; HRMS m/z 280.1216 (calcd $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$, 280.1212).



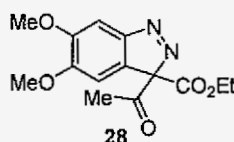
Ethyl 3-benzyl-7-methoxy-3H-indazole-3-carboxylate (24). The indicated compound was obtained in a 56% yield as a yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 1.16 (t, $J = 7.2$ Hz, 3H), 3.58 (d, $J = 13.5$ Hz, 1H), 3.79 (d, $J = 13.2$ Hz, 1H), 4.08 (s, 3H), 4.07-4.24 (m, 2H), 6.93-7.00 (m, 3H), 7.07-7.12 (m, 4H), 7.37-7.43 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.8, 40.9, 57.2, 62.4, 98.4, 113.4, 115.1, 127.0, 127.8, 130.1, 131.8, 133.4, 141.3, 146.4, 152.5, 166.8; IR (CDCl_3 , cm^{-1}) 3029, 3009, 2926, 2848, 1734, 1615; HRMS m/z 310.1322 (calcd $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2$, 310.1317).



Ethyl 3-acetyl-3H-indazole-3-carboxylate (26). The indicated compound was obtained in an 85% yield as a white solid: mp 87-89 °C; ^1H NMR (400 MHz, CDCl_3) δ 1.51 (t, $J = 7.2$ Hz, 3H), 2.88 (s, 3H), 4.56 (q, $J = 7.2$ Hz, 2H), 7.46 (td, $J = 7.2$, 0.8 Hz, 1H), 7.60 (td, $J = 8.4$, 1.2 Hz, 1H), 8.21 (dt, $J = 8.0$, 0.8 Hz, 1H), 8.46 (dt, $J = 8.4$, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.5, 23.3, 62.0, 115.7, 122.4, 124.8, 125.8, 131.1, 140.4, 140.9, 161.9, 171.7; IR (CDCl_3 , cm^{-1}) 3435, 3070, 2968, 2944, 2922, 2859, 1726, 1622, 1501; HRMS m/z 232.0350 (calcd $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_3$, 232.0347).



Ethyl 3-acetyl-5,6-dimethyl-3*H*-indazole-3-carboxylate (27). The indicated compound was obtained in an 85% yield as a white solid: mp 70-73 °C; ^1H NMR (400 MHz, CDCl_3) δ 1.51 (t, $J = 7.2$ Hz, 3H), 2.39 (s, 3H), 2.41 (s, 3H), 2.84 (s, 3H), 4.55 (q, $J = 7.2$ Hz, 2H), 7.89 (s, 1H), 8.20 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.5, 20.5, 21.1, 23.3, 61.9, 115.5, 121.6, 123.4, 135.3, 139.5, 140.5, 162.2, 171.6; IR (CDCl_3 , cm^{-1}) 3433, 3070, 2968, 2943, 2923, 2859, 1725, 1622, 1501; HRMS m/z 260.1164 (calcd $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$, 260.1160).



Ethyl 3-acetyl-5,6-dimethoxy-3*H*-indazole-3-carboxylate (28). The indicated compound was obtained in a 92% yield as a white solid: mp 169-172 °C; ^1H NMR (400 MHz, CDCl_3) δ 1.51 (t, $J = 7.2$ Hz, 3H), 2.86 (s, 3H), 3.98 (s, 3H), 4.01 (s, 3H), 4.55 (q, $J = 7.2$ Hz, 2H), 7.48 (s, 1H), 7.85 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.5, 23.1, 56.2, 56.5, 61.8, 97.1, 101.1, 118.4, 135.9, 140.1, 148.9, 152.4, 162.3, 171.8; IR (CDCl_3 , cm^{-1}) 3414, 3136, 3106, 3028, 2996, 2958, 2836, 1717, 1709, 1498; HRMS m/z 292.1062 (calcd $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_5$, 292.1059).

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CHAPTER 5. Highly Efficient Route to Fused Polycyclic Aromatics via Palladium-Catalyzed Aryne Annulation by Aryl Halides

Based on a communication published in the *Journal of the American Chemical Society*¹¹

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Abstract

Polycyclic aromatic and heteroaromatic hydrocarbons have been synthesized in high yield by two different processes involving the Pd-catalyzed annulation of arynes. The first process involves a Pd-catalyzed annulation of arynes by 2-halobiaryls and related vinylic halides. The second process utilizes a Pd-catalyzed double annulation of arynes by simple aryl halides. Both processes appear to involve the catalytic, stepwise coupling of two very reactive substrates, an aryne and an organopalladium species, to generate excellent yields of cross-coupled products.

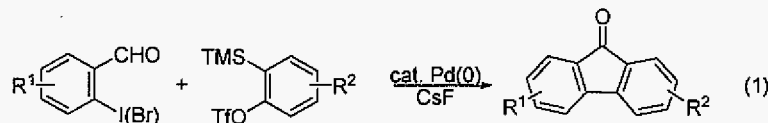
Introduction

Polycyclic aromatic and heteroaromatic hydrocarbons have been widely studied for their unique properties in material science.¹ Recently, polycyclic aromatic compounds have been discussed as potential candidates for opto-electronic devices² and as π -conjugated functional materials.^{1a} Among these, triphenylenes are the most often synthesized and widely studied. Recently, the Pd-catalyzed cyclotrimerization of arynes, generated *in situ*, has been shown to be a very novel and useful approach to the synthesis of symmetrical triphenylenes.³

However, an efficient synthesis of unsymmetrical and functionally-substituted triphenylenes remains elusive.

Transition metal-catalyzed annulation processes have proven very useful in organic synthesis.⁴ Alkynes have been frequently used as substrates for Pd-catalyzed annulations with functionally-substituted aryl and vinylic halides to synthesize a wide variety of carbocycles and heterocycles.⁵ Although there are a number of examples of stoichiometric transition metal-aryne complexes being creatively employed in organic synthesis.⁶ These very useful transition metal-catalyzed annulation processes have only recently been extended to arynes. The obvious difficulty is that arynes are very reactive substrates compared to ordinary alkynes and they readily undergo cyclotrimerization under Pd catalysis to form polycyclic aromatic hydrocarbons.^{3,7} However, the Pd-catalyzed cocyclotrimerization of arynes with alkynes,⁸ arynes with allylic halides,^{8c,9} and arynes with alkynes and allylic halides⁹ have recently been reported. All examples of the carbopalladation of arynes reported thus far have involved very stable π -allylpalladium intermediates.^{8c,9,10} The inherent instability and high reactivity of aryl and vinylic palladium species obtained by oxidative addition to Pd(0) and the high reactivity and propensity of arynes to cyclotrimerize in the presence of Pd(0) do not bode well for annulation processes requiring these species to react with one another.

Nevertheless, we have recently reported that *o*-haloarene-carboxaldehydes readily react in the presence of a Pd catalyst with arynes, generated *in situ* by the reaction of *o*-(trimethylsilyl)aryl triflates and CsF, to afford fluoren-9-ones (eq. 1).¹¹ We have also found



that 2-halobiaryls react with arynes under Pd catalysis to generate the corresponding functionalized triphenylenes in very good yields.¹² This process appears to involve the catalytic, stepwise coupling of two very reactive substrates, an aryne and an organopalladium species, to generate excellent yields of cross-coupled products. Herein, we wish to provide a full account of the scope and limitations of that process and our mechanism studies of this novel Pd-catalyzed annulation chemistry. We also wish to report for the first time the Pd-catalyzed double annulation of arynes by simple aryl halides, which affords polycyclic aromatic compounds in good yields.¹³

Results and Discussion

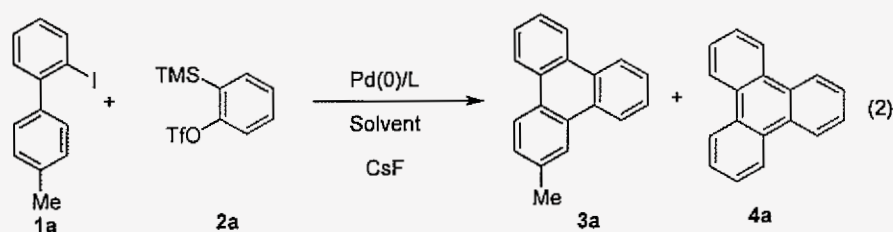
Synthesis of Fused Polycyclic Aromatics by the Pd-Catalyzed Annulation of Arynes Using 2-Halobiaryls and Related Vinylic Halides

We first allowed 2-iodo-4'-methylbiphenyl (**1a**) to react with 2.0 equiv of *o*-(trimethylsilyl)phenyl triflate (**2a**), 5 mol % of Pd(dba)₂, 5 mol % of P(*o*-tolyl)₃ and 3.0 equiv of CsF in 4.0 mL of MeCN at 110 °C for 24 h. The desired annulation product **3a** was obtained in a 12% yield and considerable triphenylene by-product was obtained (eq. 2; Table 1, entry 1). It was our hypothesis that the concentration of benzyne, which can readily undergo cyclotrimerization to generate triphenylene,³ was probably too high under these reaction conditions to allow for formation of the requisite arylpalladium halide intermediate. As a consequence, the benzyne reacted with itself in the presence of the palladium catalyst to generate a high yield of triphenylene (**4a**).

Subsequent work focused on optimization of this annulation chemistry. The key results are summarized in Table 1. During this process, we have found that the slow generation of benzyne by treatment of **2a** with CsF in the appropriate solvent system is crucial to the

success of this annulation chemistry (compare entries 1-3, 6 and 7). By increasing the amount of toluene in the MeCN/toluene solvent system, one can slow generation of the benzyne and improve the yield of the annulation product **3a**. This presumably occurs because CsF, while highly soluble in MeCN, is only poorly soluble in toluene, which in turn slows generation of the benzyne. For example, when the reaction was performed in a 1:9 ratio of MeCN/toluene, while keeping all other parameters unchanged, the corresponding annulation compound **3a** was obtained in a 92% yield with no triphenylene by-product (entry 7). However, using toluene as the only solvent provided only a trace of arene **3a**, and most of the starting materials were recovered (entry 8). We believe that MeCN may act as both a ligand and a co-solvent in our reaction system (compare entries 7 and 9). The yield of annulation product could not be improved simply by changing the ratio of the starting materials **1a** and **2a** (entries 4 and 5). If a low loading of the Pd catalyst (2 mol %) is used, the annulation product is still obtained in an 87% yield (entry 10). Other Pd catalysts, such as $\text{Pd}_3(\text{dba})_2 \cdot \text{CHCl}_3$ (entry 11), and $\text{Pd}(\text{PPh}_3)_4$ (entry 12), have also been employed in this annulation reaction, but $\text{Pd}(\text{dba})_2$ (entry 7) has given the highest yield of **3a**.

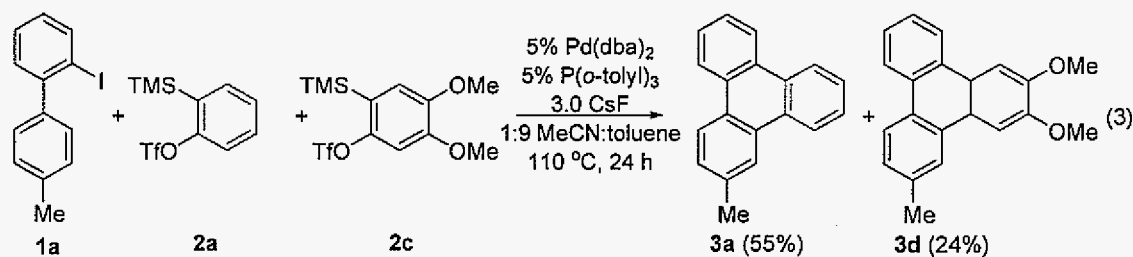
Table 1. Optimization of the Pd-Catalyzed Annulation of Benzyne (eq. 2).^a



entry	catalyst (0.05 equiv)	P(o-tolyl) ₃ (equiv)	2a (equiv)	CsF (equiv)	solvent (MeCN/toluene)	% 3a ^b	4a ^c
1	Pd(dba) ₂	0.05	2.0	3.0	100:0	12 ^d	+
2	Pd(dba) ₂	0.05	2.0	3.0	3:1	15 ^d	+
3	Pd(dba) ₂	0.05	2.0	3.0	1:1	38 ^d	+
4	Pd(dba) ₂	0.05	0.33	3.0	1:1	42	+
5	Pd(dba) ₂	0.05	5.0	5.0	1:1	30	+
6	Pd(dba) ₂	0.05	2.0	3.0	1:3	52	
7	Pd(dba)₂	0.05	2.0	3.0	1:9	92	-
8	Pd(dba) ₂	0.05	2.0	3.0	0:100	trace ^d	
9	Pd(dba) ₂	0.10	2.0	3.0	1:9	82 ^d	-
10	Pd(dba) ₂	0.02	2.0	3.0	1:9	87 ^e	-
11	Pd ₂ (dba) ₃	0.05	2.0	3.0	1:9	73	-
12	Pd(PPh ₃) ₄	0	2.0	3.0	1:9	84 ^d	-

^a All reactions were run using substrate **1a** (0.30 mmol) at 110 °C for 24 h unless otherwise specified. ^b Isolated yield. ^c +: **4a** was the major product. -: a trace amount of **4a** was detected. ^d **1a** was recovered. ^e 0.02 Equiv of Pd(dba)₂ was employed.

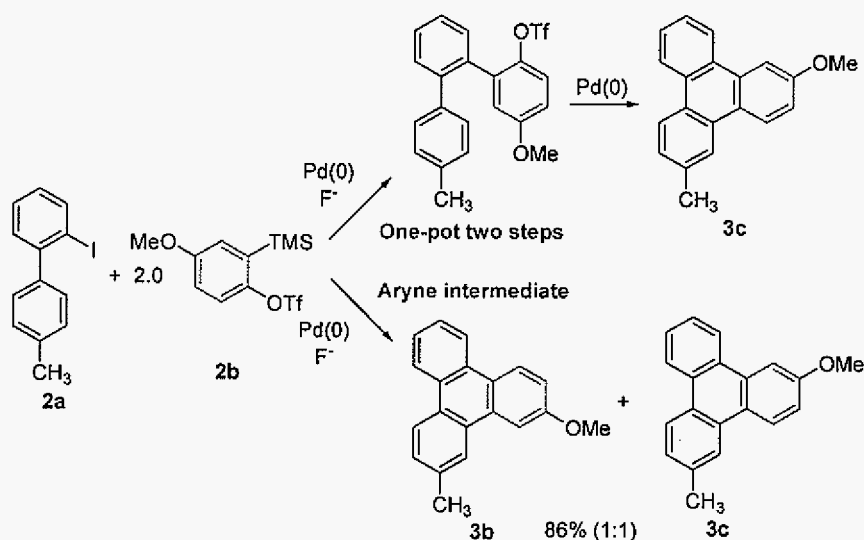
We have also examined the annulation of substituted aryne. When the 4,5-dimethoxy- and 4,5-dimethyl-substituted aryne precursors **2c** and **2d** (see Table 2 for these structures) were employed to this annulation process, we needed to increase the amount of MeCN in the solvent system in order to obtain good yields of the corresponding annulation products. We believe that generation of the aryne is significantly slower using these aryne precursors. To obtain evidence for this hypothesis, we allowed 2-iodo-4'-methylbiphenyl (**1a**) to react with 2.0 equiv of **2a** and 2.0 equiv of **2c** under our “optimal” reaction conditions. Indeed, we obtained a 55% yield of **3a** and only a 24% yield of **3d**, suggesting that benzyne itself is formed roughly twice as fast as the methoxy-substituted aryne under the same reaction conditions (eq. 3).



On the basis of the above optimization efforts, the combination of 1 equiv of the 2-halobiaryl **1a** (0.3 mmol), 2 equiv of silylaryl triflate **2a**, 5 mol % of Pd(dba)₂, 5 mol % of P(*o*-tolyl)₃, and 3 equiv of CsF in 4.0 mL of the mixed solvent (1:9 MeCN:toluene) at 110 °C for 1 d gave the best results (Table 1, entry 7). The mixed solvent needs to be changed from 1:9 to 1:3 in order to obtain good yields of the corresponding annulation products, when employing the 4,5-dimethoxy- and 4,5-dimethyl-substituted aryne precursors **2c** and **2d** in this annulation process.

Having gained an understanding of the factors that influence the Pd-catalyzed annulation process, we wanted to know whether our annulation process really involved an aryne intermediate, since another mechanism is also possible. It is conceivable that the compound 2-iodo-4'-methylbiphenyl (**1a**) and the benzyne precursor **2a** could first undergo a Hiyama cross-coupling¹⁴ to generate the terphenyl triflate, which could then undergo Pd-catalyzed cyclization to afford compound **3a**. We, therefore, allowed 2-iodo-4'-methylbiphenyl (**1a**) to react with the 4-methoxy-substituted aryne precursor **2b** to gain evidence as to which mechanism is involved. When the 4-methoxy-substituted aryne precursor **2b** was allowed to react with 2-iodo-4'-methylbiphenyl (**1a**), two isomers **3b** and **3c** were obtained in a 1:1 ratio, clearly suggesting the intermediacy of an aryne in our reaction system. The other possibility, a one pot, two step Hiyama cross-coupling, followed by intramolecular cyclization, should afford a single product **3c**,¹⁴ which is not observed (Scheme 1).

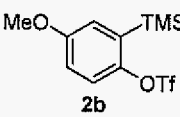
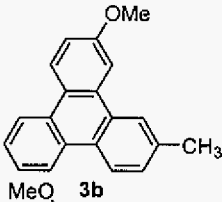
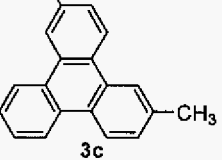
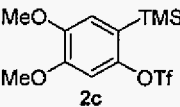
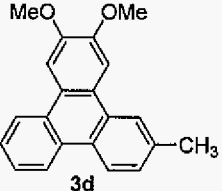
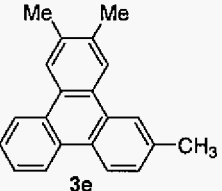
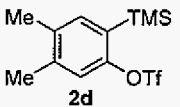
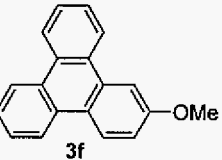
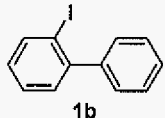
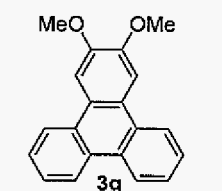
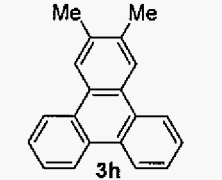
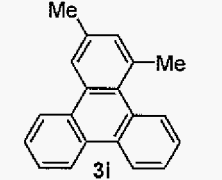
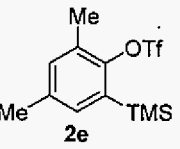
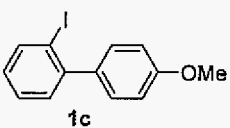
Scheme 1

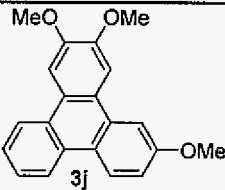
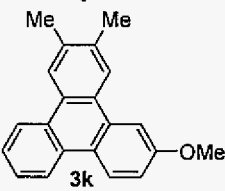
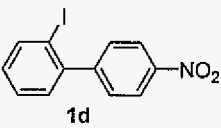
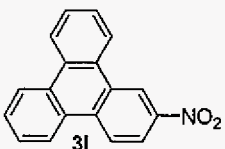
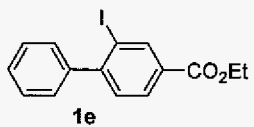
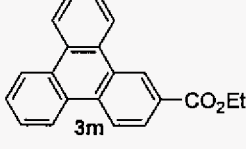
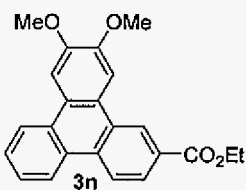
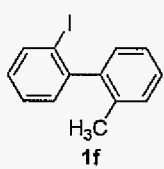
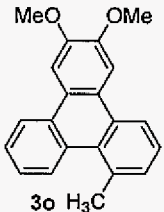
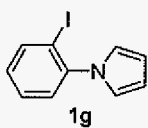
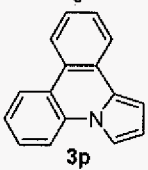
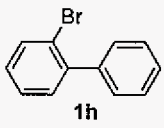
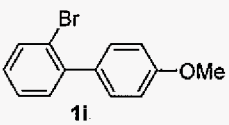


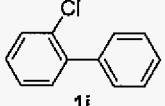
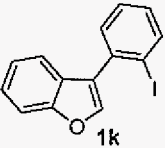
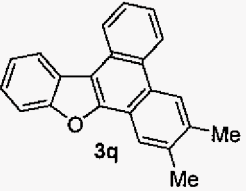
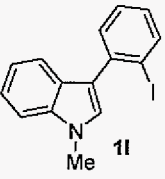
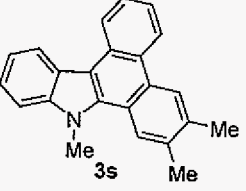
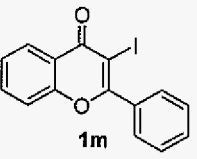
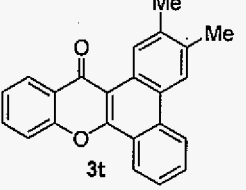
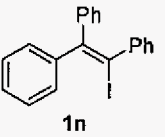
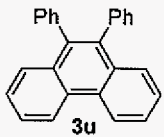
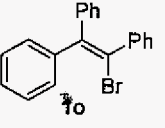
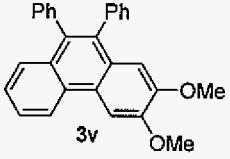
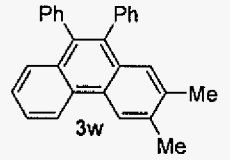
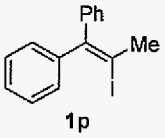
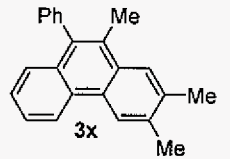
The scope and limitations of this Pd-catalyzed aryne annulation process were next examined using various aromatic and vinylic halides and aryne precursors. The results are summarized in Table 2. We first allowed 2-iodo-4'-methylbiphenyl (**1a**) to react with several different aryne precursors (**2a-d**). All of the aryne precursors work well in our annulation chemistry and give very high yields of the corresponding annulation products (entries 1-4). The parent 2-iodobiphenyl also afforded excellent yields with several aryne precursors (entries 5-8).

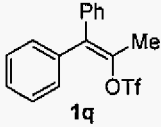
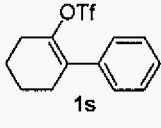
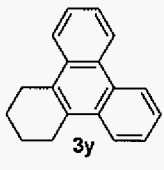
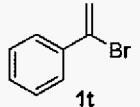
Table 2. Pd-Catalyzed Annulation of Arynes.^a

entry	substrate	aryl triflate	product(s)	% isolated yield ^b
1				92

2	1a	 2b	 3b	86 (1:1) ^c
			 3c	
3	1a	 2c	 3d	88 ^d
			 3e	
4	1a	 2d	 3f	83
5	 1b	2b	 3g	
6	1b	2c	 3h	82 ^d
7	1b	2d	 3i	
8	1b	 2e		83 ^d
9	 1c	2a	3f	

10	1c	2c		81^d
11	1c	2d		93^d
12		2a		75
13		2a		81
14	1e	2c		80^d
15		2c		38^{d,c}
16		2a		63^f
17		2c	3g	81^d
18	1h	2d	3h	79^d
19		2a	3f	75

20	 1j	2c	no reaction	0 ^e
21	 1k	2d	 3q	75 ^d
22	 1l	2d	 3s	95 ^d
23	 1m	2d	 3t	81 ^d
24	 1n	2a	 3u	92
25	 1o	2a	3u	91
26	1o	2c	 3v	92 ^d
27	1o	2d	 3w	93 ^d
28	 1p	2d	 3x	38 ^d

29	 1q	2d	3x	29 ^d
30	 1s	2a	 3y	28
31	 1t	2c	messy	0

^a All reactions were run using 0.30 mmol of the organic halide, 0.60 mmol of the aryne precursor, 5 mol % of Pd(dba)₂, 5 mol % of P(*o*-tolyl)₃ and 3.0 equiv of CsF in 4.0 mL of 1:9 MeCN:toluene at 110 °C for 24 h unless otherwise specified. ^b Isolated yield. ^c The ratio of products was determined by ¹H NMR spectral analysis. ^d MeCN:toluene = 1:3. ^e Starting material left. ^f Compound **3p** is unstable.

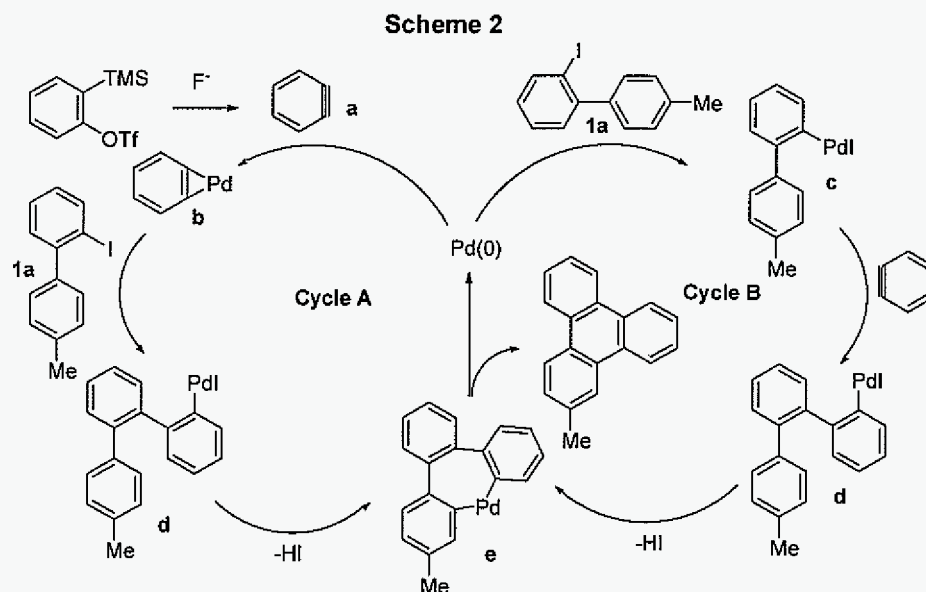
Biaryl substrates bearing both electron-donating and electron-withdrawing groups efficiently undergo this aryne annulation process to generate high yields of the corresponding polycyclic aromatics (Table 2; entries 9-14). The nitro-substituted biaryl is noteworthy, since Pd-catalyzed cyclizations onto such electron-deficient aromatic rings often proceed in significantly lower yields. When 2-iodo-2'-methylbiphenyl (**1f**) was allowed to react with aryne precursor **2c**, only a 38% yield of the corresponding annulation product was obtained (entry 15). The low yield of this reaction can be easily explained by the steric effect of the methyl group, which forces the two phenyl rings out of coplanarity, disfavoring the final cyclization step. The hetero atom-containing substrate **1g** also reacts well with the benzyne precursor **2a** to afford the anticipated annulation product **3p** in a 63% yield, although this product appears to be rather unstable. Interestingly, normally relatively unreactive 2-bromobiphenyl also reacts well with the aryne precursors **2c** and **2d** to afford the

corresponding annulation products in very good yields (entries 17 and 18). The analogous methoxy-substituted bromobiphenyl has also afforded good results (entry 19). However, 2-chlorobiphenyl proved unreactive in this annulation chemistry under the same reaction conditions (entry 20).

A number of heterocycles, including a benzofuran, an indole and a chromone, have also successfully been employed in this process, affording excellent yields of the corresponding polycyclic materials (Table 2; entries 21-23). This latter chromone substrate is particularly interesting, since it has been shown previously by us that this substrate reacts with diphenyl acetylene in the presence of a Pd catalyst to afford a furan product arising by alkyne insertion and attack of the resulting vinylpalladium intermediate on the carbonyl oxygen.¹⁵ It is also particularly noteworthy that vinylic halides, such as chromone **1m** and the simple vinylic halides **1n** and **1o**, provide excellent yields of annulation products (entries 23-27). On the other hand, vinylic iodide **1p**, and vinylic triflates **1q** and **1s** do not afford good yields of aryne annulation products under our reaction conditions (entries 28-30). It is possible that the initial vinylpalladium intermediate derived from the former substrate **1p** is undergoing rapid beta hydride elimination to generate an allene, although we have no direct evidence for this. The problem with the triflates is unclear. The vinylic bromide **1t** gave a messy reaction (entry 31). The anticipated product from vinylic bromide **1t** may simply be undergoing a further Heck reaction to produce a mixture of products.

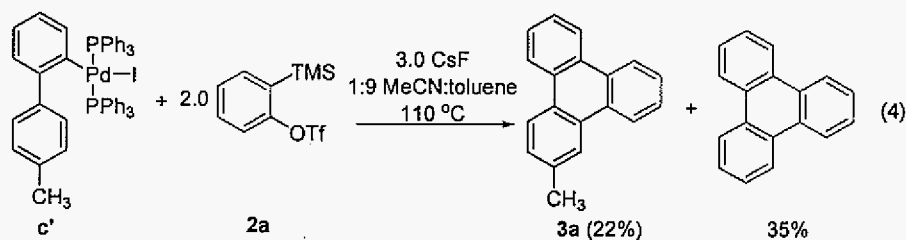
Based on the known chemistry of arynes and previous work on the Pd-catalyzed annulation of alkynes,⁵ we suggest two possible mechanisms (cycles **A** and **B**) to account for the present aryne annulation process (Scheme 2). The main difference between these two mechanisms is the first Pd oxidative addition step. In cycle **A**, the Pd(0) complex initially

undergoes oxidative cyclization with the aryne **a** to generate palladacycle **b**.¹⁶ Subsequent reaction with **1a** affords intermediate **d** [or perhaps initially an organopalladium(IV) intermediate, which undergoes rapid reductive elimination to **d**], which undergoes intramolecular C-H activation to generate the palladacycle **e**.¹⁷ Subsequent reductive elimination yields the observed annulation product **3a** and regenerates the Pd(0) catalyst. Cycle **B** involves initial oxidative addition of 2-iodo-4'-methylbiphenyl (**1a**) to Pd(0) to generate arylpalladium intermediate **c**, which then reacts with the aryne to afford the same intermediate **d** (cycle **A**), which goes on to product. Both mechanisms afford reasonable routes to the corresponding annulation product.



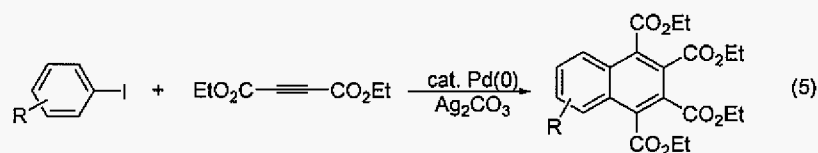
In an effort to obtain further evidence regarding the mechanism, we have prepared the palladium intermediate **c'**, illustrated in cycle **B**, by reacting 2-iodo-4'-methylbiphenyl (**1a**) with $Pd(dba)_2$ and PPh_3 .^{16c} When palladium intermediate **c'** was allowed to react with 2.0 equiv of the benzyne precursor **2a** and 3.0 equiv of CsF in the usual solvent mixture, the desired annulation product **3a** was obtained in a 22% yield, alongside a 35% yield of

triphenylene (eq. 4). While this result is consistent with the mechanism illustrated in cycle B, we still cannot rule out the mechanism shown in cycle A.

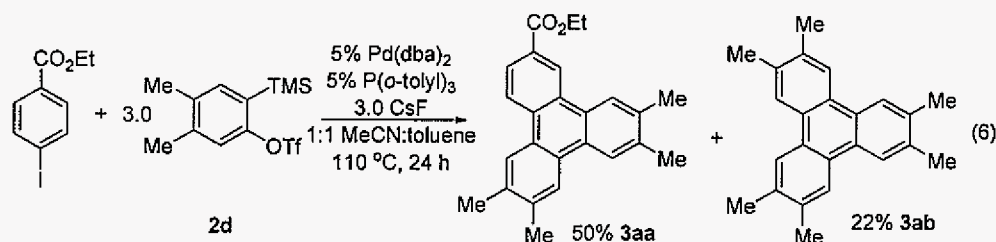


Synthesis of Fused Polycyclic Aromatics by the Pd-Catalyzed Double Annulation of Arynes Using Simple Aryl Halides

Recently, the Pd-catalyzed double annulation of an internal alkyne by simple aryl halides to synthesize multi-substituted naphthalenes has been reported (eq. 5).¹⁸ Our success in using 2-halobiaryls to annulate arynes and previous Pd-catalyzed



cyclotrimerizations³ suggested to us that we might also be able to generate polycyclic aromatics by the reaction of an aryl iodide and two arynes.¹² During the course of these studies, analogous work was reported by Jayanth and Chen.¹³ We first allowed ethyl 4-iodobenzoate to react with 3.0 equiv of the aryne precursor **2d**, 5 mol % of $\text{Pd}(\text{dba})_2$, 5 mol % of $\text{P}(o\text{-tolyl})_3$ and 3.0 equiv of CsF in 2.0 mL of MeCN and 2.0 mL of toluene at 110 °C for 24 h. The desired double annulation product **3aa** was obtained in a 50% yield, alongside 22% of the cyclotrimer **3ab** (eq. 6). Although this double annulation process only affords a 50% yield of the desired compound, it nevertheless provides a very short, efficient route to synthesize multi-substituted triphenylenes.



Subsequent work focused on optimization of this double annulation chemistry. To minimize formation of the cyclotrimer, the ratio of the MeCN to toluene solvent mixture was changed from 1:1 to 1:3. Our assumption was that increasing the amount of toluene should slow generation of the aryne and thus formation of the cyclotrimer **3ab**, while increasing the likelihood of generating the arylpalladium intermediate and thus the product **3aa**. Indeed, the reaction furnished a 58% yield of the desired product and a reduced amount of the cyclotrimer. Further changes in the ratio of the solvents failed to improve the yield of the desired double annulation product.

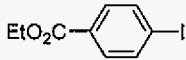
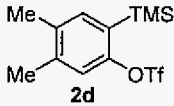
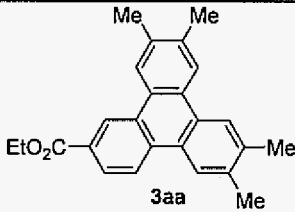
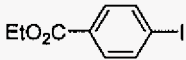
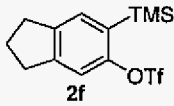
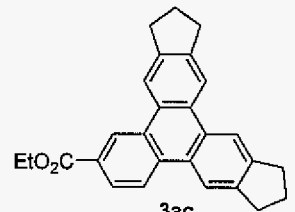
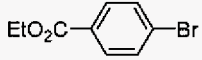
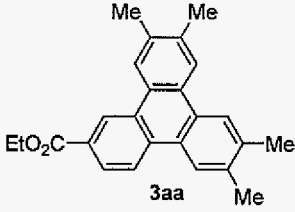
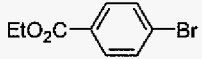
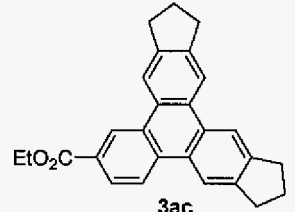
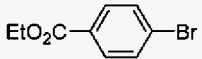
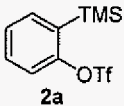
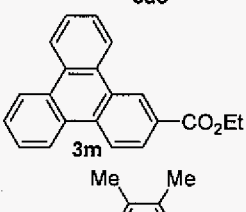
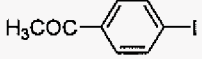
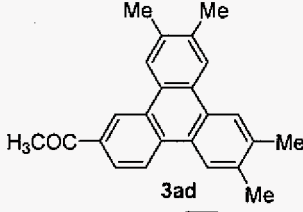
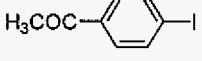
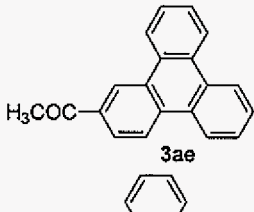
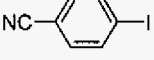
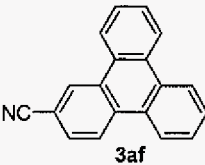
The effect of different palladium catalysts and phosphine ligands on the outcome of the reaction has also been studied. We found that Pd(OAc)₂ gave a higher yield of the desired product than other palladium catalysts, such as Pd(PPh₃)₄, Pd(dba)₂, PdCl₂(PPh₃)₂, and Pd₂(dba)₃·CHCl₃. The ligand dppf gave better results than the other ligands studied [dppe, dppp, P(*o*-tolyl)₃, PCy₃, PPh₃]. On the basis of the above optimization efforts, the combination of ethyl 4-iodobenzoate (0.3 mmol), 3.0 equiv of aryne precursor, 5 mol % of Pd(OAc)₂, 5 mol % of dppf, and 4.0 equiv of CsF, in 1.0 mL of MeCN and 2.0 mL of toluene at 110 °C for 1d gave the best yield of double annulation compound **3aa**, affording a 66% yield.

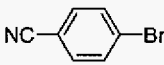
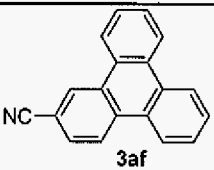
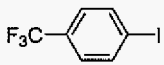
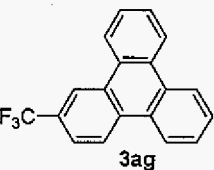
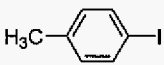
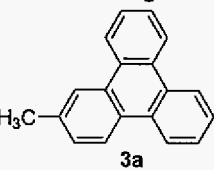
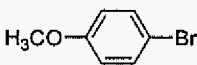
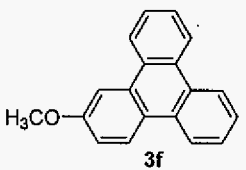
Having gained an understanding of the factors that influence the Pd-catalyzed double annulation process, we have explored the scope and limitations of this methodology. The

results are summarized in Table 3. Aryl halides bearing electron-withdrawing groups efficiently undergo this aryne double annulation process to generate moderate to good yields of the corresponding multi-substituted polycyclic aromatics (Table 3; entries 1-10). For example, ethyl 4-iodobenzoate reacts with the aryne precursor **2f** to generate the corresponding double annulation product in a 68% yield (entry 2). Interestingly, we have found that the corresponding aryl bromide, which is usually significantly less reactive than the iodide, afforded even better results (compare entries 1 and 3, and 2 and 4). For example, ethyl 4-bromobenzoate reacts with aryne precursor **2d** to produce the double annulation product **3aa** in a 76% yield (entry 3), while the corresponding iodide gave only a 66% yield. Similar results have been obtained with other substrates. We have established that the lower yield from the iodide is due to the more facile reduction of this compound to ethyl benzoate. Fagnou has also recently observed that aryl bromides can often afford better results than the corresponding iodides in palladium-catalyzed intramolecular arylation.¹⁹ Benzyne precursor **2a** can also be employed in this double annulation process, although the yields of the corresponding annulation products are a little lower than these obtained using other aryne precursors (entries 5 and 7-12). Aryl halides bearing electron-donating methyl and methoxy groups do not work well in this double annulation process (entries 11 and 12). *p*-Iodotoluene and benzyne precursor **2a** afford only a 36% yield of the annulation product. If *p*-iodoanisole is employed under our reaction conditions, a messy reaction ensues and a low yield of the desired annulation product was obtained (entry 12).

Table 3. Pd-Catalyzed Double Annulation of Arynes.^a

entry	aryl halide	silyl triflate	product	% isolated yield ^b
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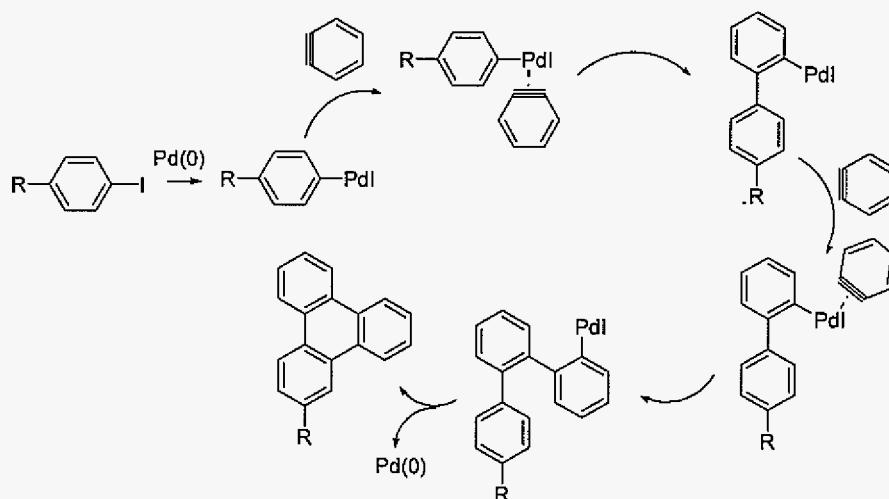
1				66
2				68
3		2d		76
4		2f		79
5				61 ^c
6		2d		54
7		2a		51 ^c
8		2a		48 ^c

9		2a		52 ^c
10		2a		43 ^c
11		2a		36 ^c
12		2a		38 ^{c,d}

^a All reactions were run using 0.30 mmol of aryl halide, 0.9 mmol of aryne precursor, 5 mol % of Pd(OAc)₂, 5 mol % of dppf, and 4.0 equiv of CsF in 4.0 mL of 1:3 MeCN:toluene at 110 °C for 24 h unless otherwise specified. ^bIsolated yield. ^cMeCN:toluene = 1:9. ^dIf *p*-iodoanisole was used, the reaction was very messy.

The mechanism shown in Scheme 3 is proposed for this Pd-catalyzed double annulation process. It consists of the following key steps: (1) oxidative addition of the aryl halide to the Pd(0) catalyst,²⁰ (2) arylpalladium coordination of the aryne and then insertion of the aryne to form a biarylpladium intermediate, (3) biarylpladium coordination to another aryne and then insertion of the aryne to form a terarylpladium intermediate, (4) intramolecular cyclization to afford a palladacyclic intermediate, and (5) reductive elimination to furnish the double annulation product and regenerate the Pd(0) catalyst.

Scheme 3



Conclusions

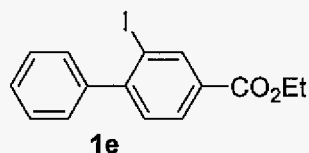
In summary, we have developed a novel, high yielding synthesis of fused polycyclic aromatics, which involves the Pd-catalyzed carboannulation of arynes by aryl and vinylic halides. This methodology provides an exceptionally efficient route to a wide variety of substituted polycyclic aromatic and heteroaromatic compounds from readily available starting materials and should find use in the construction of molecules with interesting properties and applications in material science.

Experimental Section

General. The ¹H and ¹³C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. All yields reported represent an average of at least two independent runs. Silylaryl triflate **2a** is commercially available. The substituted silylaryl triflates (**2b-e**) were prepared according to literature procedures.²¹ The product characterization data, and ¹H and

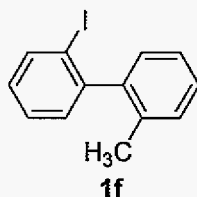
^{13}C NMR spectra for compounds **1k**, **1l**, **1m**, **3a**, **3b**, **3c**, **3d**, **3f**, **3g**, **3l**, **3q**, **3s**, **3t**, **3v**, **3aa**, and **3ab** have been reported in our previous communication.²²

Preparation of the starting materials. All 2-halobiaryls were either commercially available (**1b**, **1h**, **1j**, **1o**, and **1t**) or easily prepared from commercially available materials according to literature procedures (**1a**,²³ **1c**,²³ **1d**,²⁴ **1g**,²⁵ **1i**,²⁶ **1p**,²⁷ **1q**,²⁷ and **1s**²⁷).



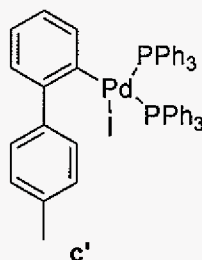
Ethyl 3-iodo-4-phenylbenzoate (1e). Compound **1e** was prepared from ethyl 3-nitro-4-phenylbenzoate.²⁸ A solution of ethyl 3-nitro-4-phenylbenzoate (1.08 g, 4.0 mmol) in a mixture of DME/EtOH/AcOH (50:40:10% by volume respectively) was added SnCl_2 (5.71 g, 30.0 mmol) and the resulting mixture was stirred at 60 °C under Ar for 16 h. The reaction mixture was diluted with diethyl ether (100 mL) and washed with 10% aq Na_2CO_3 (100 mL). The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel by using 3:1 hexanes/ethyl acetate to afford 0.87 g (90%) of ethyl 3-amino-4-phenylbenzoate as a yellow oil, which quickly decomposed as a neat liquid (no spectral data was obtained for this compound due to its instability). Ethyl 3-amino-4-phenylbenzoate was diazotized and iodinated by the following procedure. To a solution of ethyl 3-amino-4-phenylbenzoate (0.87 g, 3.6 mmol) in DME (10 mL) was added water (8 mL) containing H_2SO_4 (0.7 mL). This reaction mixture was stirred at 0 °C while NaNO_2 (0.386 g, 5.60 mmol) in H_2O (2 mL) was added dropwise over 30 min. After the addition, the mixture was stirred for an additional 20 min at 0 °C, then this mixture was added to NaI (3.0 g, 20.0 mmol) in H_2O (7 mL). Any I_2 formed was

destroyed by adding 10% aq $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) and the mixture was extracted twice with diethyl ether (30 mL). The organic layer was combined, dried (Na_2SO_4), filtered, and the solvent evaporated under reduced pressure. The residue was purified by column chromatography on a silica gel to obtain 1.06 g (78%) of the desired compound **1e** as a white solid: mp 76-77 °C; ^1H NMR (300 MHz, CDCl_3) δ 1.41 (t, $J = 7.2$ Hz, 3H), 4.40 (q, $J = 7.2$ Hz, 2H), 7.33-7.37 (m, 3H), 7.41-7.45 (m, 3H), 8.04 (dd, $J = 8.0, 1.6$ Hz, 1H), 8.61 (d, $J = 1.6$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.4, 61.4, 98.1, 128.2, 128.3, 129.0, 129.2, 129.9, 130.8, 140.6, 143.4, 150.9, 165.0; IR (CDCl_3 , cm^{-1}) 2973, 2818, 1722, 1276; HRMS m/z 351.9966 (calcd $\text{C}_{15}\text{H}_{13}\text{IO}_2$, 351.9960).



2-Iodo-2'-methylbiphenyl (1f). Compound **1f** was prepared by a procedure reported by Hart.²⁹ A solution of 2-bromoiodobenzene (1.415 g, 5.0 mmol) in THF (15 mL) was added slowly (90 min) to a solution of 2-methylphenylmagnesium bromide [prepared from 2-bromotoluene (1.71 g, 10 mmol) and Mg (0.246 g, 10 mmol) in THF (25 mL)], and the mixture was stirred under Ar for an additional 14 h at room temperature. The reaction was quenched by I_2 (3.8 g, 15 mmol), and the mixture was stirred for an additional 30 min at room temperature. The excess of I_2 was destroyed by adding 10% aq NaHSO_3 (30 mL) and the organic layer was separated and rewashed with brine (20 mL). Finally, the organic layer was dried (NaSO_4), and the solvent removed under reduced pressure. The residue was chromatographed using hexanes to afford 0.97 g (66%) of the desired compound **1f** as a clear oil: ^1H NMR (300 MHz, CDCl_3) δ 2.07 (s, 3H), 7.01-7.06 (m, 2H), 7.20-7.31 (m, 4H), 7.36-

7.40 (m, 1H), 7.92-7.94 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.1, 100.1, 125.6, 128.0, 128.1, 128.7, 129.2, 129.7, 129.9, 135.7, 138.9, 144.4, 146.8; IR (CDCl_3 , cm^{-1}) 3056, 3018, 2921, 1461, 1428; HRMS m/z 293.9910 (calcd $\text{C}_{13}\text{H}_{11}\text{I}$, 293.9906).



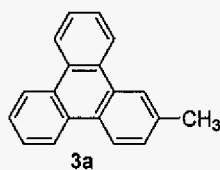
Bistriphenylphosphine 2-(*p*-methylphenyl)phenylpalladium(II) iodide (c'). Compound c' was prepared according to a procedure reported by Wenger.³⁰ A mixture of $[\text{Pd}(\text{dba})_2]$ (300 mg, 0.52 mmol), PPh_3 (574 mg, 1.14 mmol), and 2-iodo-4'-methylbiphenyl (205 mg, 0.70 mmol) in toluene (20 mL) was stirred for 1 h at room temperature and then heated for 100 °C for 5 h. The solvent was evaporated, and the pale yellow powder was washed first with a mixture of toluene (2.0 mL) and hexane (5.0 mL) and then with just hexane. Recrystallization from a CH_2Cl_2 solution layered with hexane afford a 63% yield of compound c' as a slightly yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 2.47 (s, 3H), 6.28 (t, J = 6.8 Hz, 1H), 6.51-6.60 (m, 2H), 6.95-6.98 (m, 1H), 7.10-7.32 (m, 34H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 123.1, 125.8, 127.7 (t, J = 5.3 Hz), 128.2, 128.9, 129.7, 129.8, 132.4 (t, J = 22.7 Hz), 134.8, 135.2 (t, J = 6.1 Hz), 135.3, 136.3, 138.4 (t, J = 3.3 Hz), 142.2, 145.2 (t, J = 3.8 Hz), 158.6; IR (CDCl_3 , cm^{-1}) 3140, 3051, 3030, 3002, 2985, 2919, 2859, 1479, 1433, 1093; Anal. Calcd for $\text{C}_{49}\text{H}_{41}\text{IP}_2\text{Pd}$: C, 63.62, H, 4.47. Found: C, 63.67, H, 4.59.

General Procedure for the Palladium-Catalyzed Annulation of Arynes Using 2-Halobiaryls. To a solution of the 2-halobiaryl (0.30 mmol), $\text{Pd}(\text{dba})_2$ (0.015 mmol), $\text{P}(o\text{-tolyl})_3$ (0.015 mmol), and the silylaryl triflate (0.60 mmol) in a mixed solvent system (4.0 mL)

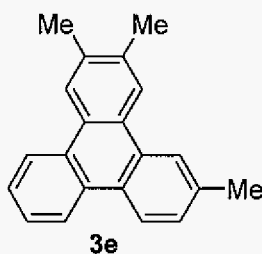
consisting of acetonitrile and toluene was added CsF (0.90 mmol). The reaction was allowed to stir at 110 °C for 24 h under Ar. The resulting solution was washed with brine (20 mL) and extracted with diethyl ether (20 mL). The combined ether fractions were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product.

General Procedure for the Palladium-Catalyzed Double Annulation of Arynes Using Aryl Halides. To a solution of the aryl halide (0.30 mmol), Pd(OAc)₂ (0.015 mmol), dppf (0.015 mmol), and the silylaryl triflate (0.90 mmol) in a mixed solvent system (4.0 mL) consisting of acetonitrile and toluene was added CsF (1.20 mmol). The reaction was allowed to stir at 110 °C for 24 h. The resulting solution was washed with brine (20 mL) and extracted with diethyl ether (20 mL). The combined ether fractions were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product.

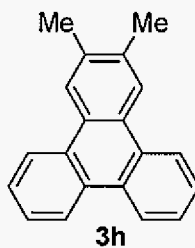
Characterization data:



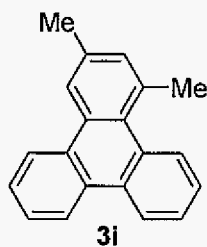
2-Methyltriphenylene (3a). The indicated compound was obtained in a 92% yield (66.8 mg) as a white solid: mp 100-102 °C (lit.¹⁸ mp: 101-103 °C); ¹H NMR (300 MHz, CDCl₃) δ 2.56 (s, 3H), 7.42 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.44-7.57 (m, 4H), 8.39 (s, 1H), 8.47 (d, *J* = 8.4 Hz, 1H), 8.54-8.62 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 137.1, 130.1, 130.0, 129.9, 129.6, 128.9, 127.7, 127.4, 127.3 (2C), 127.0, 123.6, 123.5 (2C), 123.4, 123.3, 22.1; IR (CDCl₃, cm⁻¹) 3081, 3026, 2923, 2854, 1742, 1437; HRMS *m/z* 242.1098 (calcd C₁₉H₁₄, 242.1095).



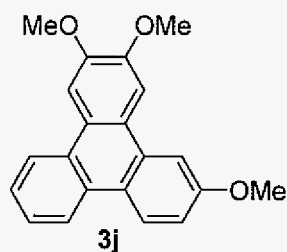
2,3,6-Trimethyltriphenylene (3e). The indicated compound was obtained in a 98% yield as a white solid: mp 134-135 °C; ^1H NMR (300 MHz, CDCl_3) δ 2.48 (s, 6H), 2.59 (s, 3H), 7.41 (d, $J = 7.2$ Hz, 1H), 7.56-7.59 (m, 2H), 8.34-8.37 (m, 3H), 8.45 (d, $J = 8.7$ Hz, 1H), 8.55-8.59 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.5, 22.1, 123.2, 123.3, 123.3, 123.4, 124.0, 124.1, 126.8, 126.9, 127.4, 128.0, 128.2, 128.3, 129.6, 129.8, 130.0, 136.2, 136.3, 136.8; IR (CDCl_3 , cm^{-1}) 3006, 2959, 2938, 2856, 1655, 1509; HRMS m/z 270.1412 (calcd $\text{C}_{21}\text{H}_{18}$, 270.1408).



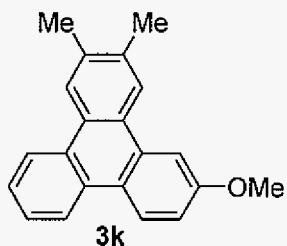
2,3-Dimethyltriphenylene (3h). The indicated compound was obtained in an 83% yield as a white solid: mp 158-160 °C (lit.³¹ 158-160 °C); the ^1H and ^{13}C NMR spectra match the literature data.³¹



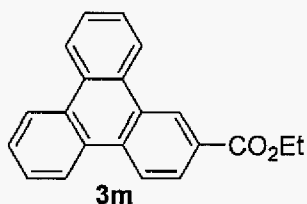
1,3-Dimethyltriphenylene (3i). The indicated compound was obtained in an 84% yield as a white solid: mp 91-93 °C; ^1H NMR (300 MHz, CDCl_3) δ 2.59 (s, 3H), 3.04 (s, 3H), 7.36 (s, 1H), 7.58-7.66 (m, 4H), 8.35 (s, 1H), 8.59-8.67 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 21.8, 26.8, 121.5, 123.3, 123.4, 123.9, 125.8, 126.4, 127.2, 127.4, 128.3, 128.5, 130.3, 130.6, 130.9, 131.1, 131.6, 133.4, 135.5, 136.0; IR (CDCl_3 , cm^{-1}) 3016, 2963, 2948, 2864, 1651; HRMS m/z 256.1256 (calcd $\text{C}_{20}\text{H}_{16}$, 256.1252).



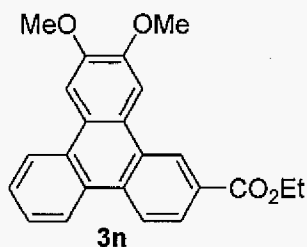
2,3,6-Trimethoxytriphenylene (3j). The indicated compound was obtained in an 81% yield as a white solid: mp 149-150 °C; ^1H NMR (300 MHz, CDCl_3) δ 3.95 (s, 3H), 4.02 (s, 3H), 4.04 (s, 3H), 7.14 (dd, $J = 9.0, 2.4$ Hz, 1H), 7.51-7.54 (m, 2H), 7.68 (s, 1H), 7.71 (d, $J = 2.4$ Hz, 1H), 7.82 (s, 1H), 8.33-8.37 (m, 1H), 8.43-8.46 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.6, 56.0, 56.1, 104.5, 106.0, 114.3, 122.9, 123.0, 123.3, 123.8, 124.7, 125.1, 126.2, 126.4, 128.6, 129.4, 131.0, 149.3, 149.5, 158.8; IR (CDCl_3 , cm^{-1}) 3098, 3063, 3002, 2957, 2936, 2834, 1613; HRMS m/z 318.1262 (calcd $\text{C}_{21}\text{H}_{18}\text{O}_3$, 318.1255).



6-Methoxy-2,3-dimethyltriphenylene (3k). The indicated compound was obtained in a 93% yield as a white solid: mp 143-144 °C; ^1H NMR (300 MHz, CDCl_3) δ 2.42 (s, 6H), 3.96 (s, 3H), 7.15 (dd, $J = 9.0, 2.4$ Hz, 1H), 7.51-7.54 (m, 2H), 7.91 (d, $J = 2.4$ Hz, 1H), 8.18 (s, 1H), 8.28 (s, 1H), 8.43-8.54 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.5, 20.6, 55.7, 105.7, 115.4, 122.9, 123.2, 123.7, 124.0, 124.1, 125.1, 126.3, 126.9, 127.8, 128.5, 128.9, 129.8, 131.4, 136.2, 136.5, 159.0; IR (CDCl_3 , cm^{-1}) 2962, 2938, 2916, 2838, 1640, 1617; HRMS m/z 286.1361 (calcd $\text{C}_{21}\text{H}_{18}\text{O}$, 286.1357).

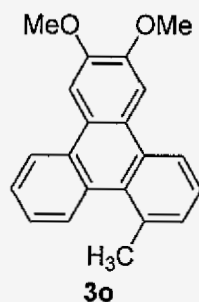


Ethyl triphenylene-2-carboxylate (3m). The indicated compound was obtained in an 81% yield as a white solid: mp 128-130 °C (lit.³² 129-130 °C); the ^1H and ^{13}C NMR spectra match the literature data.³²

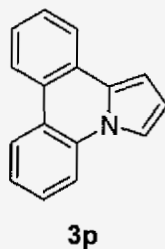


Ethyl 10,11-dimethoxytriphenylene-2-carboxylate (3n). The indicated compound was obtained in an 80% yield as a white solid: mp 132-134 °C; ^1H NMR (300 MHz, CDCl_3) δ 1.49 (t, $J = 7.2$ Hz, 3H), 4.04 (s, 3H), 4.06 (s, 3H), 4.49 (q, $J = 7.2$ Hz, 2H), 7.54-7.62 (m, 2H), 7.73 (s, 1H), 7.76 (s, 1H), 8.07 (dd, $J = 8.4, 1.8$ Hz, 1H), 8.31 (d, $J = 7.8$ Hz, 1H), 8.45-8.50 (m, 2H), 8.94 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.7, 56.0, 56.2, 61.4, 104.3, 104.5, 122.9, 123.4, 123.9, 124.1, 124.3, 124.8, 126.1, 126.4, 128.0, 128.4, 128.5, 129.1, 130.4,

132.4, 149.6, 149.7, 167.1; IR (CDCl₃, cm⁻¹) 3063, 2980, 2936, 2907, 2838, 1710, 1514; HRMS *m/z* 360.1366 (calcd C₂₃H₂₀O₄, 360.1361).

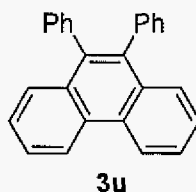


6,7-Dimethoxy-1-methyltriphenylene (3o). The indicated compound was obtained in a 38% yield as a white solid: mp 140-142 °C; ¹H NMR (300 MHz, CDCl₃) δ 3.06 (s, 3H), 4.11 (s, 3H), 4.12 (s, 3H), 7.45-7.65 (m, 4H), 7.95 (s, 2H), 8.38 (d, *J* = 7.5 Hz, 1H), 8.50 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.63 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 27.1, 56.2, 104.5, 105.2, 120.8, 122.8, 124.5, 124.8, 124.9, 126.3, 126.6, 128.8, 129.9, 130.3, 130.8, 131.0, 131.2, 135.7, 149.6, 149.7; IR (CDCl₃, cm⁻¹) 3021, 2962, 2936, 2914, 2834, 1613, 1513; HRMS *m/z* 302.1311 (calcd C₂₁H₁₈O₂, 302.1306).

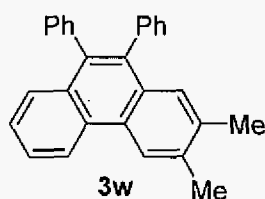


Pyrrolo[1,2-*f*]phenanthridine (3p). The indicated compound was obtained in a 63% yield as a white solid: mp 152-153 °C; ¹H NMR (300 MHz, CDCl₃) δ 6.72 (t, *J* = 3.6 Hz, 1H), 6.95 (dd, *J* = 3.6, 1.5 Hz, 1H), 7.33-7.53 (m, 4H), 7.76 (q, *J* = 1.5 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 8.00 (dd, *J* = 7.5, 1.2 Hz, 1H), 8.23 (d, *J* = 7.5 Hz, 1H), 8.32 (dd, *J* = 8.1, 0.9 Hz,

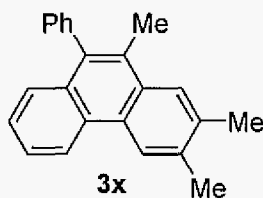
1H); ^{13}C NMR (75 MHz, CDCl_3) δ 102.2, 112.4, 113.3, 115.2, 121.9, 122.7, 123.0, 124.0, 124.2, 125.0, 126.1, 126.5, 128.3, 128.7, 129.5, 133.4; HRMS m/z 217.0895 (calcd $\text{C}_{16}\text{H}_{11}\text{N}$, 217.0891).



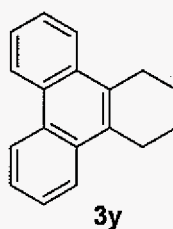
9,10-Diphenylphenanthrene (3u). The indicated compound was obtained in a 92% yield as a white solid: mp 236-238 °C (lit.³³ 236-237 °C); the ^1H and ^{13}C NMR spectra match the literature data.³³



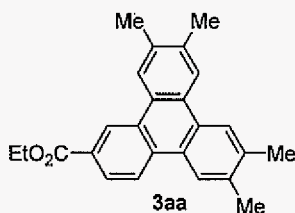
2,3-Dimethyl-9,10-diphenylphenanthrene (3w). The indicated compound was obtained in a 93% yield as white solid: mp 229-230 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.37 (s, 3H), 2.58 (s, 3H), 7.18-7.30 (m, 10H), 7.35 (s, 1H), 7.48 (t, $J = 7.2$ Hz, 1H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.66 (t, $J = 7.2$ Hz, 1H), 8.61 (s, 1H), 8.82 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.5, 20.8, 122.5, 123.2, 126.3, 126.4, 126.6, 126.7, 127.8, 128.0, 128.1, 128.6, 129.9, 130.6, 131.3, 131.4, 131.8, 135.9, 136.5, 137.0, 140.0, 140.1; IR (CDCl_3 , cm^{-1}) 3053, 3026, 2972, 2941, 2916, 1489, 1428; HRMS m/z 358.1727 (calcd $\text{C}_{28}\text{H}_{22}$ 358.1721).



2,3,10-Trimethyl-9-phenylphenanthrene (3x). The indicated compound was obtained in a 38% yield as a white solid: mp 119-120 °C; ^1H NMR (300 MHz, CDCl_3) δ 2.28 (s, 3H), 2.41 (s, 3H), 2.48 (s, 3H), 7.10 (s, 1H), 7.27-7.30 (m, 2H), 7.44-7.65 (m, 5H), 8.09-8.12 (m, 1H), 8.47 (s, 1H), 8.71-8.75 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 17.5, 20.4, 20.6, 122.9, 123.0, 125.2, 126.2, 126.5, 127.1, 127.7, 127.9, 128.6, 129.0, 129.9, 130.6, 131.0, 131.8, 135.0, 135.8, 136.9, 141.2; IR (CDCl_3 , cm^{-1}) 3062, 3021, 2972, 2860, 1476; HRMS m/z 296.1569 (calcd $\text{C}_{23}\text{H}_{20}$, 296.1565).

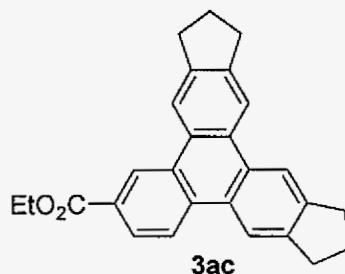


1,2,3,4-Tetrahydrotriphenylene (3y). The indicated compound was obtained in a 28% yield as a white solid: mp 121-123 °C (lit.³⁴ 121-122 °C); the ^1H NMR spectra matches the literature data;³⁴ ^{13}C NMR (75 MHz, CDCl_3) δ 23.1, 27.1, 122.9, 123.5, 125.7, 126.8, 129.4, 130.5, 132.2; IR (CDCl_3 , cm^{-1}) 3073, 2935, 2872, 2848, 1435; HRMS m/z 232.1255 (calcd $\text{C}_{18}\text{H}_{16}$, 232.1252).

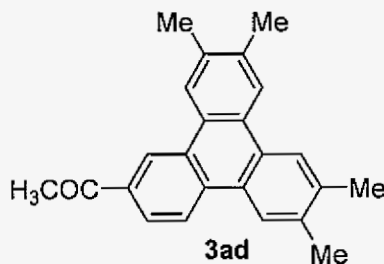


Ethyl 6,7,10,11-tetramethyltriphenylene-2-carboxylate (3aa). The indicated compound was obtained in a 66% yield (71 mg) as a white solid: mp 148-150 °C; ^1H NMR (300 MHz, CDCl_3) δ 1.48 (t, $J = 7.2$ Hz, 3H), 2.41 (s, 3H), 2.42 (s, 3H), 2.43 (s, 3H), 2.45 (s, 3H), 4.48 (q, $J = 7.2$ Hz, 2H), 8.08-8.18 (m, 4H), 8.29 (s, 1H), 8.46 (d, $J = 8.7$ Hz, 1H), 9.17 (d, $J = 1.2$

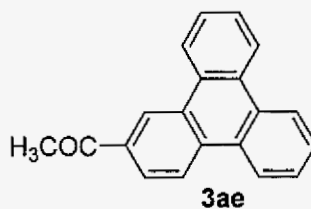
Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.3, 137.3, 136.6, 136.0, 135.8, 133.0, 129.2, 128.8, 128.1, 128.0, 127.4, 126.9, 126.6, 125.2, 124.5, 124.1, 123.7, 123.6, 123.1, 61.3, 20.6, 20.5, 20.4 (2C), 14.7; IR (CDCl_3 , cm^{-1}) 3019, 2874, 2918, 1710, 1612; HRMS m/z 356.1781 (calcd $\text{C}_{25}\text{H}_{24}\text{O}_2$, 356.1776).



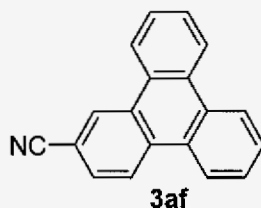
Ethyl 1,2,3,10,11,12-hexahydrodicyclopenta[*b,h*]triphenylene-6-carboxylate (3ac). The indicated compound was obtained in a 68% yield as a white solid: mp 251-253 °C (lit.³² 253-255 °C); the ^1H and ^{13}C NMR spectra match the literature data;³² HRMS m/z 380.1780 (calcd $\text{C}_{27}\text{H}_{24}\text{O}_2$, 380.1776).



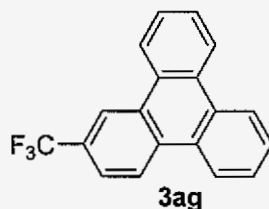
1-(6,7,10,11-Tetramethyltriphenylene-2-yl)ethanone (3ad). The indicated compound was obtained in a 54% yield as a white solid: mp 236-238 °C (lit.³² 236-238 °C); the ^1H and ^{13}C NMR spectra match the literature data;³² HRMS m/z 326.1674 (calcd $\text{C}_{24}\text{H}_{22}\text{O}$, 326.1670).



1-(Triphenylene-2-yl)ethanone (3ae). The indicated compound was obtained in a 51% yield as a white solid: mp 154-155 °C (lit.³² 152-153 °C); the ¹H and ¹³C NMR spectra match the literature data;¹³ HRMS m/z 270.1049 (calcd C₂₀H₁₄O, 270.1044).



Triphenylene-2-carbonitrile (3af). The indicated compound was obtained in a 48% yield as a white solid: mp 215-217 °C (lit.³⁵ 215-216 °C); ¹H NMR (400 MHz, CDCl₃) δ 7.68-7.82 (m, 5H), 8.53-8.66 (m, 5H), 8.89 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 110.7, 119.6, 123.4, 123.6, 123.7, 124.1, 124.4, 127.9, 128.0, 128.3, 128.4, 128.5, 128.6, 129.1, 129.2, 130.1, 130.3, 130.9, 133.1; IR (CDCl₃, cm⁻¹) 2955, 2919, 2851, 2225, 1659; HRMS m/z 253.0894 (calcd C₁₉H₁₁N, 253.0891).



2-(Trifluoromethyl)triphenylene (3ag). The indicated compound was obtained in a 43% yield as a white solid: mp 115-117 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.63-7.71 (m, 4H), 7.81 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.57-8.63 (m, 4H), 8.67 (d, *J* = 8.8 Hz, 1H), 8.83 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 120.8 (q, *J* = 4.1 Hz), 123.3 (q, *J* = 3.3 Hz), 123.5, 123.6, 123.6, 123.9, 124.2, 124.7 (q, *J* = 270.5 Hz), 127.7, 127.8, 128.2, 128.9, 129.1, 129.2, 129.8, 130.2, 130.6, 132.3 (q, *J* = 1.2 Hz); IR (CDCl₃, cm⁻¹) 3026, 2979, 2943, 2920, 1446; HRMS m/z 296.0817 (calcd C₁₉H₁₁F₃, 296.0812).

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GENERAL CONCLUSIONS

In this dissertation, very reactive intermediate arynes, which can be generated under mild reaction conditions, have been employed in a variety of novel, synthetically useful reactions, such as insertion and Pd-catalyzed annulation chemistry. A wide variety of *N*-arylated amines, sulfonamides and *O*-arylated phenols and carboxylic acid, carbazoles, dibenzofurans, triphenylenes, and other polycyclic aromatic and heteroaromatic hydrocarbons have been synthesized using these new methods.

Chapter 1 describes an efficient, transition-metal free procedure for the *N*-arylation of amines, sulfonamides and carbamates and *O*-arylation of phenols and carboxylic acids by allowing these substrates to react with a variety of *o*-silylaryl triflates in the presence of CsF. This method accommodates a variety of functional groups.

Chapter 2 investigates the Pd-catalyzed, one-pot, two-step synthesis of a variety of carbazoles and dibenzofurans starting with the corresponding *o*-iodoanilines or *o*-iodophenols and *o*-silylaryl triflates. The scope and limitations of this process have been studied. By using this methodology, the carbazole alkaloid muckonine can be synthesized in a very good yield.

Chapter 3 reports the first, efficient, mild, transition metal-free method for the intermolecular C-N σ -bond addition of amides and S-N σ -bond addition of sulfinamides to arynes to form one C-C bond and one heteroatom-carbon bond in one step at room temperature. Evidence for a stepwise mechanism is provided.

Chapter 4 presents an efficient method to synthesize a variety of indazoles via a [3+2] cycloaddition of diazo compounds with silylaryl triflates in the presence of CsF or TBAF under very mild reaction conditions.

Chapter 5 describes a novel palladium-catalyzed annulation of arynes by aryl halides, which provides a novel way to synthesize a variety of polycyclic aromatic and heteroaromatic hydrocarbons in good yields. This process involves a first catalytic, stepwise coupling of two very reactive substrates, an aryne and an organopalladium species, to generate excellent yields of cross-coupled products. Evidence for a stepwise mechanism is provided.

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